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REASONS FOR THE USE OF CARBON DIOXIDE WITH OXYGEN IN THE TREATMENT OF PNEUMONIA*

BY YANDELL HENDERSON, PH.D.†

THE use of oxygen in the treatment of pneumonia is becoming common. Prevention of cyanosis is an important measure for conserving the patient's strength and avoiding the vicious circle into which a progressively developing asphyxia otherwise leads. Both theory and general experience are in favor of early and continuous inhalational treatment of pneumonia, even though precise statistical proof of its benefit is still lacking.

The use of carbon dioxide with oxygen is also finding an increasing number of advocates among those who have used it. Inhalation of a mixture of these two gases generally recommends itself chiefly on the ground of its obvious beneficial effects upon both respiration and the circulation. The broad theoretical basis upon which this therapy rests seems not as yet to be appreciated to the degree requisite for its most effective use. The purposes of this paper are, first, to set forth the fundamental reasons for this therapy and the advantages that it offers when the inhalation, which tends to augment respiration, is combined with administration of morphine or other narcotic drugs, most of which tend to depress respiration; and, secondly, to describe a tent with which the inhalation may be conveniently applied.

PREVENTION AND RELIEF OF ATELECTASIS

During several years past I have received a large number of reports of an informal character regarding the use on pneumonia patients of the inhalator which Haggard and I[1] introduced for the resuscitation of the victims of carbon monoxide asphyxia. It appears that many physicians have found that 5 or 7 per cent. carbogen (5 per cent. carbon dioxide and 95 per cent. oxygen, or 7 per cent. carbon dioxide and 93 per cent. oxygen) which these inhalators contain is not only effective in overcoming cyanosis, but also as a stimulant in the depression resulting from acute pneumonic conditions.

Especially during the past two years treatment by inhalation of carbogen, either by means of the H-H Inhalator or with such a tent as that to be here shown, has been given an extensive trial by the medical department of the Brooklyn Edison Company under the direction of Dr. J. J. Wittmer[2]. The results reported indicate, and more recent extensive unpublished experience confirms, that inhalation of carbogen affords the same benefit in overcoming cyanosis as does oxygen and has the additional advantage of inducing also a deeper and often a slower rate of breathing.

Up to the present time, however, the most important application of inhalation of carbon dioxide has been for the prevention, rather than the treatment, of pneumonia. For the prevention of secondary pneumonias carbon dioxide is indeed the one great specific that nature offers[3]. In health the lungs are kept constantly expanded and their airways open. Through these tubes they are the best-drained organs in the body. The force which keeps them open is the tonus of the diaphragm and the other muscles of the thorax. Whenever this tonus is lowered, as it is after anesthesia, asphyxia, and immersion, and especially after abdominal operations, as well as in elderly and debilitated patients long confined to their beds, the vital capacity of the lungs is greatly diminished. In the unaerated areas mucus accumulates until some of the airways are filled and closed. If there happens to be present also inhaled foreign material, or mucus from catarrhal inflammation, these conditions also contribute to the blocking of airways. As soon as any part of a lung is thus shut off, the air within it is absorbed into the blood; for the total pressure of all the gases in the venous blood is always forty to sixty millimeters less than the total pressure in the arterial blood, which is the same as in open areas of the lung, and the same as in the outside air[4]. The occluded lung or lobe or lobules are soon collapsed, and in such collapsed areas any bacteria that happen to be present find conditions favorable for their growth and activity. This conception of the part that atelectasis plays in the development of pneumonia, first clearly stated by Coryllos and Birnbaum[5], is now established. It is essentially in this way that all secondary pneumonias develop.

This conception assigns to the tonus of the skeletal muscles of the body a place of prime

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importance in respiration. It is this tonus that keeps the lungs expanded and prevents atelectasis. The movements of respiration do not consist merely in the alternate contraction and relaxation of the thoracic muscles. In reality, these muscles pass at each breath from one tonus level to another and back again. When respiration is depressed the tonus of the entire musculature of the body is depressed also. The capacity of the thorax is greatly decreased by the relaxed and elevated diaphragm and the flaccidity of the other respiratory muscles. In the partially deflated lungs atelectasis readily develops; and, if infection is present, pneumonia results. The common sequence is lowered muscular tonus, decreased vital capacity, occlusion, atelectasis, pneumonia.

When, on the contrary, respiration is stimulated, as it is in normal muscular activity by an increased production of carbon dioxide in the body, or as it is by inhalation of carbon dioxide, the tonus of all the muscles of the body, and especially those involved in respiration, is increased. The lungs are expanded, occlusion of airways is prevented, and any parts that have already been occluded are reopened. The normal drainage from the lungs through the airways is maintained, or reëstablished, and the development of a secondary pneumonia is prevented.

With these points in mind it is easy to understand why it is that, until recently, massive collapse of a lung and the consequent development of postoperative pneumonia have been among the principal hazards of surgery; and why it is that in surgical clinics which have adopted as a routine procedure the full dilation of the lungs by inhalation of carbon dioxide after all major operations, such pulmonary complications are effectively prevented[6].

Essentially the same considerations apply to the pneumonia of the newborn[7] which, until recently, has caused the death within the first month of life of an average of four out of each hundred babies. In nearly all of these cases the infection starts in areas of the lung which have remained in the prenatal state of atelectasis. The ancient practice, continued down to the present time, has been to make the baby cry at least once daily by means of some painful stimulus with the idea that this exertion would induce dilation of these areas in the lungs. Such efforts, however, have done little to decrease the huge neonatal mortality from pneumonia. Now, however, in maternity hospitals where inhalation of carbon dioxide mixed either with oxygen or air is employed to induce deep breathing the mortality from this cause has been greatly decreased or altogether eliminated.

The same treatment is now being tried as a means of clearing the lungs and controlling the spasms of coughing after pertussis[8]. If the favorable results that have been obtained in the few cases thus far treated prove general, it appears probable that by this means the frequency of secondary pneumonia, which now often follows pertussis and is responsible for a large part of its mortality, will be considerably diminished.

In the pneumonias originating in influenza and other nose and throat infections or in chill and other conditions that bring patients to the medical wards of hospitals, the element of atelectasis is not as yet so fully recognized. Surgeons, by the habit of their minds, have been ready to accept the idea that occlusion is a critical factor in such an infection as pneumonia, and that drainage should be an important, or even essential, measure of cure. They tend to think of an infection in terms of an abscess. Physicians, on the other hand, by the habit of their minds, are little inclined to appreciate the importance of occlusion as a morbid factor, or of drainage as a measure of relief. They tend to think of pneumonia in the same terms that they use for typhoid or diphtheria, and to look for a prophylaxis and therapy along similar lines.

It is a significant fact that no one has yet reported the cure of an experimentally induced pneumonia by means of a vaccine, a serum or an antitoxin. On the other hand, experimental pneumococcic pneumonia has been cured with carbon dioxide. In studies upon pneumonia in dogs, which were carried out in this laboratory three years ago[9], the evidence obtained from x-ray pictures of the chest was decisive that occlusion of the affected area is a factor of critical importance in determining the course of the disease. When deep breathing was induced by placing the animals in an atmosphere containing about 7 per cent. carbon dioxide, the infected and occluded areas in the lungs were opened up and drainage through the bronchi and trachea was reëstablished. The pneumonia in most cases rapidly cleared up and the animals promptly recovered.

Investigators who have devoted years of work to studies of the various types of pneumococci and to the development of corresponding sera for pneumonia are sometimes inclined to draw a distinction between pneumonia as it occurs in the medical wards and the pneumonias that, until recently, developed in the surgical wards, and to argue that the treatment should be different. But, even if there were legitimate grounds for such a distinction, the element of occlusion is none the less important also in medical pneumonia. Thus Lord[10] remarks: "In the course of pneumonia there is at times a plugging of the bronchi with consequent absorption of air and the trapping of infectious material in that part of the lung supplied by the occluded passage. This undesirable com-

plication is prone to occur in patients who are allowed to lie constantly on one side. It can to some extent be avoided by turning the patient frequently from the back to one or the other side during the course of the disease."

This recommendation is exactly that which has been customary among surgeons in dealing with pneumonia in their cases before the superior advantages of inhalation of carbon dioxide were recognized. It is therefore in the highest degree probable that in medical pneumonia, no less than in postoperative pneumonia, the most effective means of inflating and clearing an occluded lung or lobe is the increased depth of breathing and general improvement of muscular tonus and circulation induced by inhalation of carbon dioxide.

NARCOTICS, ESPECIALLY MORPHINE, WITH INHALATION OF CARBON DIOXIDE

Pneumonia patients commonly exhibit degrees of excitement varying from restlessness to delirium of such intensity as sometimes to require forcible restraint. Aside from their suffering, their excitement involves a physical strain that seriously depletes vitality. Largely on this account it is the orthodox practice in England, where pneumonia is an even more common and severe disease than with us, to administer morphine almost as a routine treatment. In addition there is in England a general belief that this drug affords fundamental, and not merely symptomatic, benefit in pneumonia. In the next section of this paper reasons not heretofore recognized in support of this belief will be set forth.

Here it is to be emphasized only that the one accompanying disadvantage of morphine and other narcotic drugs is that by depressing respiration they may increase anoxemia and cyanosis. This disadvantage is, however, overcome and eliminated when the lightly morphinized or otherwise narcotized patient receives enough carbon dioxide by inhalation to induce deep full respiration. Restlessness and excitement are thus controllable by narcotics without depression of respiration or increase of cyanosis.

BACTERICIDAL AND RESOLVING ACTION OF CARBONIC ACID

There are yet other reasons for combining morphine and carbon dioxide in the treatment of pneumonia.

The principal physiologic effect of morphine and of some other narcotics is to raise the threshold of the respiratory center for carbon dioxide[11]. This means that respiration under morphine automatically decreases the volume of air breathed per minute to such an extent that, as the amount of carbon dioxide produced in the body is unaltered, a much higher concentration of carbon dioxide is maintained in the lungs even when there is no carbon dioxide in the inspired air. When in addition the patient breathes air containing an appreciable amount of carbon dioxide, the concentration of carbon dioxide in the lungs may be increased from the normal 5 per cent. to 6 or 7 per cent. or more; amounts corresponding to, or somewhat exceeding, those in the lungs during moderate physical exercise, but without its hyperpnea.

The peculiar rôle that carbon dioxide plays in the fluids and tissues of the body is often misinterpreted. It is a common but serious error to think that carbon dioxide, because it becomes carbonic acid in solution, must be similar in its effects to those of any other acid. Actually the rôle of carbon dioxide in the fluids of the body is fundamentally different from that of all other acids. One of the most important contributions to modern biochemistry was that of L. J. Henderson[12] who showed that carbonic acid normally exists as a free acid in the blood and also that it is the only acid that can ever so exist. If, for instance, instead of inhalation of carbon dioxide, hydrochloric acid were ingested, the results reached would be in most essential respects diametrically opposite with the two acids. Strong acids when introduced into the body through the stomach are immediately neutralized by the sodium bicarbonate of the blood. The blood alkali (generally called the alkaline reserve) is thus reduced, and the carbon dioxide thus liberated is exhaled through the lungs. If the administration of acid is pushed too far, both the combined and free carbon dioxide or carbonic acid in the blood and also that it is the only acid acidosis, in the sense of an acid poisoning, may be induced. On the other hand, when carbon dioxide is inhaled, particularly in a morphinized man or animal, not only is the carbonic acid of the blood increased, but there may develop also an increase of the blood alkali through some as yet incompletely understood readjustment between the blood and tissues. In both cases the pH of the blood is lowered; but one decreases the blood alkali while the other tends to increase it[13].

With these conceptions in mind we may next consider two other points in favor of the use of carbon dioxide in combination with oxygen and with morphine or other narcotic or respiratory depressant drugs. These are (1) the bactericidal power of carbonic acid upon the pneumococcus and (2) the promotion of solution in the pneumonic exudate by carbonic acid. Lord[10] has particularly stressed the fact that ". . . the pneumococcus has biologic peculiarities which may be concerned in its behavior as an infectious agent. It is very sensitive to a change in the reaction of media in which it grows. Its extreme sensitiveness to acid may be better appreciated when it is stated that the range be-

tween the slightly alkaline reaction of normal blood and that of the culture containing glucose in which death of the organism takes place is about that between ordinary tap water and distilled water standing in the laboratory. . . .As the inflammatory process in the lung goes through its evolution . . . the reaction, so far as we can learn from animal experiment and tests of the lung immediately after death, changes from slightly alkaline to a degree of acidity within the range of the acid death point of the pneumococcus. . . . At an acidity corresponding to that which the inflammatory process may reach, the duration of life of the pneumococcus in fluid culture media without serum is only about two hours. . . . In explanation of the factors contributing to recovery from a chemical point of view it may be conceived that as the evolution of the local process takes place with an increase of acidity . . . the acid death point of the pneumococcus is reached".

As regards the influence upon resolution of the pulmonic exudate of even a slight acidity Lord further remarks, "Two enzymes are demonstrable in the pneumonic lung, one active in slightly alkaline, neutral, and slightly acid media and another with optimum activity in still more acid media. As the evolution of the pneumonic process takes place there is an increase in cells containing ferment, a diminution of serum containing anti-ferment, and a shift to an acid reaction. . . . Increase of cells (enzymes), diminution of serum (anti-enzymes), and a shift to an acid reaction thus permit the melting away of the exudate and restoration to normal."

In addition to the statements thus quoted it may be pointed out that, although carbonic acid is a very weak acid, its acidity in media not too heavily buffered with protein and salts is sufficient to reach the degree (that is the lowering of pH) requisite for at least partial inhibition of the growth of the pneumococcus, and for promoting resolution of the pneumonic exudate. It affords the sole means that present scientific knowledge appears to offer for attack upon the pneumococcus along the line here indicated. But in order to exert an effective bactericidal and resolving action carbon dioxide inhalation needs the assistance of morphine or some other respiratory depressant drug.

THE CARBOGEN TENT

Of the four methods of administering inhalational treatment to pneumonia patients the tent seems to be establishing itself as generally the best. Intranasal insufflation is generally much less effective in overcoming cyanosis and involves considerable waste of gas. A mask held over the face is irksome to a feverish suffocating patient. Oxygen chambers are expensive and involve a serious fire hazard.

Several tents are now offered on the authority of experienced investigators and reliable manufacturers; but perfection and standardization of the best model have not yet been attained. In particular the problem of cooling the recirculated atmosphere of the tent and condensing the surplus moisture from it is one that is both of special importance and difficulty. The tent here shown, which has been developed

Figure: Showing carbogen tent and cylinder with reducing valve and pressure gauges, from which the gas passes through a small tube at the top of the figure and is injected into the large tube above the tent. A circulation is thus induced through the cooler filled with ice from which the air cooled, dried, and enriched with oxygen and carbon dioxide passes into the tent again through a large tube back of the patient's pillow. The nurse is shown taking a sample of the atmosphere of the tent for analysis with the syringe analyzer recently described by L. A. Greenberg and the writer[15].

through the advice and coöperation of Dr. H. W. Haggard and the writer with the firm that makes it[14], has distinct advantages in this respect as well as in simplicity of construction.

It involves no motor or blower but produces circulation by means of a thermo-syphon and simple injector. Air is thus drawn out of the top of the tent and returned to it back of the patient's pillow. For cooling, the atmosphere is passed through broken ice or over a container of "dry ice" (carbon dioxide snow) vented to the outside. While this tent can be used conveniently for inhalation of oxygen alone, it is designed particularly for the administration of a mixture of oxygen and carbon dioxide, now generally and conveniently termed "carbogen". For the administration of such mixtures of gases most of the other tents now available have an inadequate cooling and condensing capacity. Inhalation of carbon dioxide, by increasing the volume of breathing, increases the amount of heat that the patient gives off through his breath. It thus tends to reduce the patient's temperature, provided that the tent, in which it is administered, has a sufficient cooling and condensing power; otherwise the temperature in the tent rises to an uncomfortable degree. Economy in the consumption of

oxygen or carbogen is an important element in keeping down the expense of the treatment.

Careful tests have shown that with a flow of gas, whether oxygen or carbogen, of 7 liters per minute a circulation is induced sufficient to pass the entire atmosphere of the tent through the cooler in two minutes. The concentration of oxygen in the tent is usually about 50 per cent., which is generally sufficient to overcome cyanosis and is as high as is generally considered advisable. When oxygen alone is used the atmosphere contains from 1.6 to 2 per cent. of carbon dioxide from the patient's breath. When 7 per cent. carbogen is used the carbon dioxide atmosphere of the tent, because of diffusion to the outside air, varies between 4.5 and 5 per cent. These amounts are sufficient to induce deep but not excessive breathing. The temperature under the tent is from 3 to 7 degrees Fahrenheit cooler than in the room in which the tent is placed. The humidity of the atmosphere in the tent is usually from 44 to 57 per cent. The windows of the tent are cellophane, a much less inflammable material than celluloid, and are made large so as to avoid a sense of isolation and imprisonment in the patient.

CONCLUSIONS

The advantages afforded by the use of carbon dioxide together with oxygen in the inhalation treatment of pneumonia are as follows:

(1) Deeper breathing is induced which prevents the development of occlusion and tends to open parts of the lungs already occluded.

(2) Under inhalation of carbon dioxide, morphine or other narcotic drugs may be used more freely to counteract excitement and restlessness. The stimulus to respiration afforded by carbon dioxide tends to counteract the depression of breathing which such drugs otherwise induce.

(3) Carbon dioxide in solution becomes carbonic acid and tends to exert a bactericidal action upon the pneumococcus and a resolving action upon the pneumonic exudate. These effects are best obtained when inhalation of carbon dioxide is combined with administration of morphine or other narcotic and respiratory depressant drugs. While carbon dioxide tends to lower the pH of the blood and of the pneumonic exudate, it does not decrease the blood alkali or tend to induce an acidosis, but rather the contrary.

The tent here shown while suitable for the treatment of pneumonia patients with oxygen is specially designed for their treatment with carbogen, a mixture of carbon dioxide and oxygen.

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BEQUESTS BY DR. HOWE

By the will of Dr. Octavius T. Howe, who died on December 26, the Addison Gilbert Hospital of Gloucester receives a bequest of $500. In all $17,000 was left in public bequests.

ONE OUT OF TWELVE IN HOSPITAL EACH YEAR

According to a survey prepared by Dr. Allon Peebles for the Committee on the Costs of Medical Care, more than 10,000,000 persons, or about one in twelve inhabitants of the country are treated each year in the hospitals of the United States. There are available more than 900,000 beds, including those for mental and tuberculosis cases, and more than 49,000 bassinets for newly born infants. For every 100 hospital beds in cities ranging from 100,000 to 300,000 in population there are two internes, seven graduate nurses, twenty-nine student nurses and two attendants. All told, the industry of curing illness and maintaining health employs nearly 1,500,000 persons in the United States.

NEW ENGLAND SURGICAL SOCIETY

COLITIS RESULTING IN OBLITERATION OF THE LUMEN OF THE INTESTINE*

BY F. B. LUND, M.D.†

THE treatment of chronic ulcerative colitis is and has been for years an unsatisfactory matter. The very term colitis covers a multitude of sins. It is employed frequently in a wrong sense for various colonic dysfunctions. We have toxic colitis, mucous colitis, nervous colitis, and last but not least the imaginary colitis so universally treated by quacks by colonic irrigations. Then there is the true ulcerative colitis in which the ulcers, as seen by the proctoscope, are surrounded by edematous mucous membrane. It is characterized by a great deal of mucus, constant diarrhea, emaciation, exhaustion, and frequently anemia. In its early stages it is amenable to medical treatment, consisting of a bland, non-irritating diet and carefully regulated life. At first, nothing but water can be given. The disease, however, has frequently existed for a considerable time before the physician is consulted, and is frequently not amenable to medical treatment. If such treatment is to be successful, it must be continued for a very long time, in an especially careful manner. In long existing cases, the complications which occur are the development of polypi, hemorrhage, and strictures. Sometimes where the disease is in the lower sigmoid and upper rectum, ischiorectal abscesses and fistulas may develop.

A few years ago the treatment consisted chiefly of colonic irrigations with various antiseptics, chiefly nitrate of silver. Cecostomy or appendicostomy was done to facilitate such irrigation. These operations were never very successful in my hands. The treatment by colonic irrigation at least in the Mayo Clinic was given up for a vaccine treatment. They claim to have isolated a diplostreptococcus as the cause of the disease, from a culture of which a vaccine was prepared, and favorable results followed its use, as compared with the colonic irrigations. There still were many resistant cases which dragged on to a fatal issue. They have developed a treatment with immune horse serum, which was at first unsatisfactory on account of the serious sickness resulting from its use. They now have isolated certain antibodies from the serum with which they claim to have been successful in entirely relieving twenty-four out of fifty cases of their symptoms. Extensive cases in which the entire colon was involved, and cases in which complications such as polypi or strictures have developed, became surgical, as they always have done.

For resistant cases, in my belief there is still no better treatment than ileostomy, by complete division of the ileum with suture and dropping back of the lower end. This of course puts the colon completely at rest, the distressing diarrhea stops or greatly diminishes. After the operation the cases are examined from time to time with the proctoscope, and the ulcers may be seen to heal. After they have healed so far as can be seen by the proctoscope, and there have been no symptoms for several months, it may be safe to reconnect the ileum and put the patient back into the normal condition. I have several times carried out these procedures with entirely satisfactory results, no return of symptoms, gain in weight, and continued good health. Such results, however, may not always occur, and the case I am going to report is an evidence of that fact.

Mrs. M. B., aged 27, had an ulcerative colitis which had existed for about a year. She was exhausted, emaciated and very weak. Numerous rather superficial ulcers could be seen by the proctoscope. She had had long-continued treatment under the supervision of Dr. Franklin W. White in the outpatient department and wards of the City Hospital. Her diarrhea and pain were not relieved. She had lost twenty-two pounds and the outlook for her was bad. On July 9, 1923, at the City Hospital I did an ileostomy. At the operation the cecum was found yellow, thickened by fibrin deposits, and congested. A similar condition of less degree was shown in the transverse and descending colon. It was evident therefore that the disease was most active in the upper colon, and probably least in the sigmoid, where the ulcers were observed. She rapidly recovered from the operation, gained in weight, was able to perform all the duties of a housewife for eight years, having only an occasional discharge of mucus (sometimes a little bloody) from the rectum. She was seen from time to time by me and examined with the proctoscope, but the ulcers, though smaller, never healed to such an extent that we thought it safe to reconnect the divided ileum. She was under Dr. White's observation from time to time. On April 5, 1931, I found her in the ward at the Carney Hospital, having grown very thin and having developed a large abdominal tumor, in the left upper abdomen and flank. Her loss of weight had been twelve pounds. The tumor was hard, not tender and not movable. She had some cramp-like pains in the abdomen and profuse bleeding from the rectum. The pain came in waves, resembling peristaltic pains. The red blood count was a little over two thousand. We naturally concluded that she had developed a cancer on top of her old colitis, and she and I were both willing as a last resort to attempt operation. After a preliminary transfusion, a left rectus incision was made and the tumor was found to be an enormously edematous and contracted omentum, having wrapped up in it a tremendously thickened and contracted transverse colon, descending colon and splenic flexure. The ascending colon was also obliterated and in a like condition. The cecum itself was not contracted, though much thickened, and the sigmoid appeared normal. A glance at the figure will show the extensive obliteration of the colon which had resulted from eight years of inflammation, although the organ was physiologically at

*Read at the annual meeting of the New England Surgical Society, Portland, Maine, September 11, 1931.

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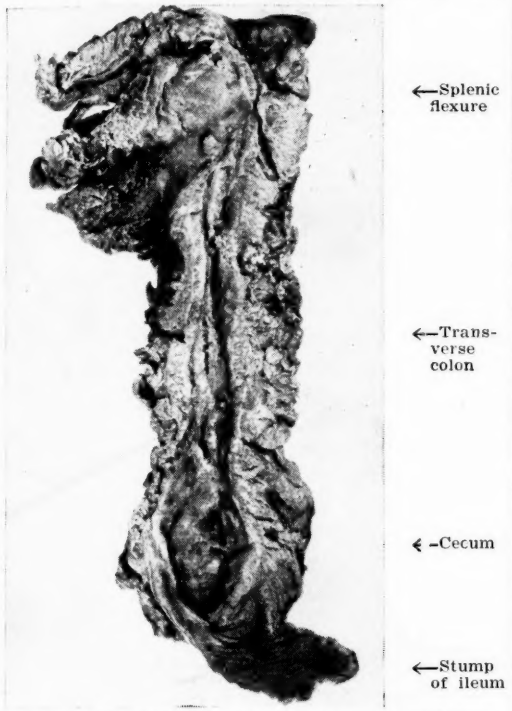
rest. We see reports of strictures, abscesses and perforations of the colon in colitis, but I never yet saw such extensive obliteration. A small probe was all that would go through the lumen. The colon was removed without difficulty, except for the excessive edema of the omentum and mesocolon, which made it difficult to place the ligatures in the splenic region. The incision was sutured in the usual manner and a small gauze drain was carried into the splenic region through a stab wound in the flank. After the operation a second transfusion was done. The patient went home in three weeks, is attending to her work, has gained fourteen pounds and feels well.



Colon removed, after hardening and contracture of specimen.

The case is reported as showing:

1. That a patient may be practically well and at work for eight years, with an ileostomy, although the colitis for which it was performed has never healed; in fact, is going on to extensive contraction and obliteration.

2. That removal of the colon may be successfully performed in very anemic patients with the aid of transfusion, repeated if necessary.

3. The remarkable degree of contraction and obliteration shown by,

4. the presence of a large, hard, adherent tumor, which proved to be inflamed omentum. This I never saw reported in a case of colitis.

5. The cheerful and successful way in which the patient managed an ileostomy for eight years.

NOTE: I might consider uniting the ileum to the sigmoid if I were sure the latter was free from disease. It looked all right, but I am doubtful. The patient gets along so well with her ileostomy that she has almost forgotten there is any other way.

DISCUSSION

DR. D. W. PARKER, Manchester, N. H.: I feel very much flattered to be asked to open the discussion on this paper. My position is analogous to that of the patient who went to the doctor's office for examination and was told after the examination that she needed a major operation and that a general anesthetic would be necessary, and she said to the doctor, "How long will it be before I know anything?"

He said, "Madam, you must not expect too much from the anesthetic." (Laughter.)

I know very little of this condition. I think most of us have at some time been cursed with one of these severe cases of colitis and many of us, whatever treatment we have instituted, have wished we had done the other thing.

My experience with a case of this kind has been limited to one single case and in fact I am not particularly proud of myself on that. This was a man about forty years old who developed a tumor in the right iliac fossa. He was not in very good condition but, contrary to my expectations, when I opened him up, he stood the operation very, very badly. I didn't feel justified in doing even a biopsy. He had glands all along the mesentery.

I expected him to die. He was very unhappy, but he didn't die. I thought I made a mistake and thought he was tuberculous. The patient went to see Dr. David Cheever and he took it out later and perhaps he can tell us more about it.

Dr. Lund, did I not see this case which you reported, at your office some time ago?

DR. LUND: That woman? Yes.

DR. PARKER: She was quite happy and very grateful to Dr. Lund, and I think he is to be congratulated on his results.

DR. LINCOLN DAVIS, Boston, Mass: *Mr. President and Gentlemen*—I feel myself very much in the same situation that Dr. Parker spoke of. I am really not qualified at all to talk on the subject of colitis and surgical treatment of it because I have always tried to avoid these operations, since I felt that they were on the whole pretty unsatisfactory, and I have always insisted on very prolonged medical treatment before attempting to do anything about it by surgery. Any operation which is an indirect attack on a disease, such as ileostomy, I think is an unsatisfactory operation.

This case of Dr. Lund's is a very unusual one and a very brilliant one, and very few of us have had anything to compare with it.

I have my feeling in regard to ulcerative colitis. One reason that I feel surgical treatment is unsatisfactory is because of a patient I had many years ago, who was going downhill and demanded that something be done. The patient had a prolonged course of medical treatment before I did an ileostomy and found the colon considerably thickened beyond that point.

She continued to go downhill rapidly after the operation. She had a discharge of mucus and blood from the ileostomy and finally died in the hospital, and the autopsy showed a seri-

ous ulceration above the point of the ileostomy in the ileum.

Another case I should like to speak of, something like Dr. Lund's, was of a man who had very severe colitis, was taking large doses of morphine without any benefit and was going downhill. He had been treated for a long time and had great loss of weight and about twenty movements or more a day. I did an ileostomy on him and it gave only very partial relief.

A few months later he came back and said he was having a lot of tenesmus and frequent discharges of mucus and pus from the rectum, and that he had the ileostomy in addition and didn't feel any better than before.

We carried him along for a year or so that way and then the tenesmus became so extreme that I attempted to remove his large intestine and did remove it from the ileum to the peritoneal reflection of the rectum, and the specimen was examined by the late Dr. Homer Wright, who finally, after very careful sections found tubercle bacilli in the ulcerations.

I told the man that later on we would perhaps be able to connect the ileum to the rectum and reëstablish his alimentary canal. This was seven or eight years ago. He has been quite well. He is a plumber and has been quite successful in his business.

He came to me a while ago to see if I could do anything about reëstablishing the canal. On examination I found the rectum practically obliterated, a very narrow canal. You could hardly insert your finger into it. The scar tissue was contracted so there was no possibility of doing a reconstruction operation.

So, altogether I feel that although ileostomy is an operation of some value and we have to have recourse to it at times, we surely ought to give the medical treatment, particularly the serum treatment, a very thorough trial before resorting to it.

Dr. F. H. Lahey, Boston, Mass.: I should particularly like to speak about this subject because we have had something over thirty-five ulcerated colitis cases, and I think it is an extremely serious and difficult problem to deal with from the surgical point of view.

There is no unanimity of opinion regarding the Bargen bacillus. He has claimed a certain specificity of the so-called Bargen bacillus culturally and as to its production of ulcerative intestinal lesions in animals, and Paulson has contended that this is not consistently true. I think we must all have in mind that everyone who deals with ulcerative colitis knows that it is a peculiar disease and that patients with this disease often show unexplained cessation or activation of the lesions and oftentimes I think recoveries may be just part of the natural course of the disease. Certainly, until there is more definite agreement among the bacteriologists and gastroenterologists regarding Bargen's bacillus and serum, I think we have to withhold judgment.

Hearst in London, an extremely sound gastroenterologist, has claimed splendid results with dysentery serum.

We must not think because we live in a temperate zone that amebic dysentery does not occur. We almost always have a case of it in the hospital on our Gastro-enterologic Service and it is not uncommon throughout New England.

Dr. Craig of the Army Medical School says that when you have a four-plus positive serum reaction, that means you have amebic dysentery and Dr. Kiefer has been able to demonstrate the ameba in a considerable number of our ulcerative colitis cases. One must consider always in the medical treatment of these cases the possibility of an underlying amebic dysentery and the use of emetine, yatren and other antiamebic drugs in the medical management of certain cases of ulcerative colitis.

Regarding the surgical condition, we have found it extremely difficult to select just the right time at which to do an ileostomy. One does not want to give a patient a permanent ileostomy if it is avoidable because it is a very undesirable enterostomy. Yet, if you let them go too long with a septic colon, by the time you do the ileostomy, they die.

There are some very important points regarding the technique of ileostomy for ulcerative colitis. You should not handle the colon. These patients die from two things, septic emboli and peritonitis. With this condition, one has a badly infected colon. The small veins close to the mesentery of the colon are all thrombosed, the wall of the colon is infiltrated with organisms, and the resistance of the peritoneum is low. Many of the cases will die of peritonitis just as a result of the trauma secondary to handling the colon. You should pick the ileum up with the least possible trauma, do the ileostomy as delicately as possible and not touch the colon at all.

If the lesion is serious enough to demand ileostomy, it is a destructive lesion in the colon (this is well illustrated by Dr. Lund's case), and there will be but few of these cases in which it will be proper to reëstablish the alimentary stream after ileostomy. Some of these cases, in our experience, show recurrences and reactivation with discharge of blood, mucus and pus even after ileostomy.

We have recently had a most sad situation in a young girl who had a very acute ulcerative colitis. We did an ileostomy because of her extremely toxic state. She gained thirty pounds, her temperature came to normal and she became perfectly well. She pestered us, however, to put her fecal stream back by closing her ileostomy but we refused and urged her not to

have it restored. She went back to a western city where she lived, and succeeded in persuading a surgeon there to do it and she died in three days.

I think you have to have in mind in patients with ulcerative colitis

1. The possibility of the presence of an underlying amebic infection.
2. That it is extremely important to select the proper time and not wait too long before doing the ileostomy; and
3. That when lesions are so severe as to demand ileostomy, the colon is usually so badly destroyed that one should seriously hesitate to restore the fecal stream.

DR. ERNEST L. HUNT, Worcester, Mass: Apropos of living comfortably with a colostomy, I have a lady on whom I did a right-sided colostomy. She is the wife of a veterinary surgeon in a nearby city, and she has had such perfect management of it that she is quite satisfied with it. The only time it ever got away from her was on one occasion when she got excited at a horse race and then it let go.

I have had no experience with the Craig test that Dr. Lahey mentioned, but our hospital was fortunate enough about two years ago to acquire as a pathologist a young man who had considerable experience in the Near East and it was not long before we picked up some amebic cases. Altogether we have had five, two of which presented surgical aspects.

The first one was a very chronic case in an elderly man who suddenly developed fairly acute abdominal symptoms and, feeling somewhat at sea as to what it could be, we were a little conservative about it, finally explored and found a perforation high up in the small intestine.

So far as I know, that is the only case, that happens to be on record, which has perforated at that point in the bowel, though I have not made an exhaustive search of the literature. He died of peritonitis.

The other case was one of a lady of fifty-five who had developed mucus and bloody stools, had lost weight and had grown rather pale. She had been through a careful set of examinations including x-ray studies by a very capable x-ray man and had been advised to have an exploratory operation as there was evidence which was interpreted as early carcinoma of the lower bowel.

The stool that she passed was shown me, and being interested in amebae, I sent it to the laboratory and it was reported as positive. The x-ray study which we had made showed only in the lower colon, the lower part of the descending colon and part of the sigmoid, a lack of haustration, what they call the "lead pipe" appearance.

The woman was put on the usual treatment for that condition, emetin subcutaneously, later followed by yatren. Her symptoms promptly disappeared and four months later the x-rays showed normal haustration and normal action of the bowel.

After a check-up three months later our x-ray man said there was no appearance which could be interpreted as cancer. She has not been operated upon and is well.

DR. DAVID CHEEVER, Boston, Mass: *Mr. President,* I hadn't meant to enter into the discussion. Dr. Parker spoke of a patient, who, by the way, was an Armenian. He said he didn't get another chance at him because he consulted Dr. Cheever. As I have had something to do with the Ethics and Discipline Committee of the Massachusetts Society, I should say that this patient was urged by me to go back to Dr. Parker. To this he expressed his entire satisfaction and his entire willingness, but some diffidence on account of the fact that he had not paid Dr. Parker's bill.

DR. PARKER: Since, he is in bankruptcy.

DR. CHEEVER: The patient had a large tumor, and I operated, having been assured so far as possible that my bill would be paid. I found it was a massive tuberculoma of the cecum which is often quite justifiably mistaken by the operator for carcinoma. He made a good recovery and has written several very, very grateful letters but a certain diffidence has prevented his coming back to my office for personal observation.

DR. F. B. LUND: I didn't say anything about differential diagnosis. One ought to think hard about tuberculosis and amebic dysentery. I have had several cases of restoration of the continuity after enterostomy, which were fortunately successful. One I kept in the hospital for seven months before the restoration. She has been perfectly well for eight or nine years. The only trouble is that she has grown enormously fat, which, after all, shows that the condition is cured.

This case illustrates, however, that after an ileostomy these processes may go on without interruption in spite of the fact that the colon is physiologically at rest.

I have been interested in finding it stated in the literature that after ileostomy the lower ileum takes on the drying function the colon ordinarily has, so that the patient has hard stools which could be regulated as well with ileostomy as with a colostomy.

I have had that experience in only one case. All the others had liquid stools. The patient whose case I have just reported has a very efficient apparatus with metal instead of rubber in it, and although she has liquid stools, she is perfectly happy and contented. She is so well satisfied with her present condition and gain in weight that we are not considering ileosigmoidostomy. I am not sure that the sigmoid is entirely free of disease either, which must be proved before that is done.

A STUDY OF 102 CASES OF ATROPHIC ARTHRITIS

II. Constitutional Defects

BY MILLARD SMITH, M.D.*

A COMPARISON of literature on chronic arthritis of the past and present centuries is of interest. The turning point in the trend of this literature came at the beginning of the present century, because at this time the theory of infection in relation to this disease was reaching its maturity. It is very unfortunate that such an important theory should have had the effect of subordinating investigations of physiologic deviations from the normal to those of focal infection and the bacteriology of affected joints. Infection in relation to arthritis is of the utmost importance, but nevertheless, the subject should not be approached from this aspect primarily as apparently is done with but few exceptions today. Much of significance is lost when this latter route is followed too closely. There are many important observations awaiting the use of sight, hearing and touch.

Jones[1] has presented a most accurate clinical account of atrophic (rheumatoid) arthritis, in which these various manifestations of the disease are set forth with significant emphasis. It is the purpose of this paper to report the occurrence of similar findings in a group of 102 cases of the disease. Certain preliminary data upon these cases have been given in the preceding paper[2].

The observations which are to be reported represent deviations from the normal in the general physiology of these subjects. They emphasize the constitutional aspects of the disease, and hold little promise for such limited theories as are based upon the idea that infection of the joints accounts for the etiology of the condition. They also point the way to a more liberal theory of the disease; this has been presented in another paper[3].

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FAMILIAL TENDENCY TO ATROPHIC ARTHRITIS

It is common knowledge that arthritis, or rheumatism, shows strong familial tendencies. This fact must be reckoned with in any theory of the disease. Pemberton and Peirce[4] elicited a family history of the disease in 58 per cent. of a series of 142 patients. They suggest that this familial tendency is greatest in asthenic subjects.

TABLE I

INCIDENCE IN CASES OF THIS SERIES GIVING FAMILY HISTORY OF ARTHRITIS IN RELATION TO PHYSICAL TYPES

	Female			*Male*		
	Asthenic	Intermediate	Sthenic	Asthenic	Intermediate	Sthenic
Number denying F. H.	16 (a)	9 (c)	9 (d)	8 (f)	6 (g)	5
Number giving F. H.	7 (b)	5	5 (e)	9	3	3 (h)
Incidence per 100 with F. H.	30	36	36	53	33	37

(a) One patient's father has asthma.
(b) One patient has sister with arthritis, and maternal grandfather has asthma.
(c) One patient has a sister with urticarial attacks, another sister with psoriasis, and a brother with asthma.
(d) One patient's mother has psoriasis.
(e) One patient has an aunt with arthritis, another aunt with hay fever.
(f) One patient's mother has severe migraine. Another patient's father and mother and daughter have attacks of urticaria.
(g) One patient's sister has eczema. Another patient's maternal uncle has asthma.
(h) One patient's three sisters and one brother have attacks of urticaria, and a maternal uncle had acute rheumatic fever.

Table I presents these data for the present series. The incidence among the asthenic males almost approaches the general incidence of the series of Pemberton and Peirce. The average incidence of the entire group of 85 patients in whom this factor was investigated is 37.5 per cent. Taken together with the findings of these previous observers, this is a matter of definite significance.

It is of interest to note (Table I) the occurrence of allergic manifestations in other members of certain of these families. These data taken alone are hardly extensive enough to be of significance, but in view of other findings in these patients which will follow, they may indicate an inherited tendency to great reactibility. The records indicate that a careful history was taken to show the presence or absence of allergic manifestations at some time in the lives of both the patients and their families in 39 instances. The data are tabulated for these cases in Table II. It suggests an important line of investigation in this disease.

PAST HISTORY OF ALLERGIC MANIFESTATIONS

The incidence of a past history of allergic manifestations was ascertained in 91 patients of the series. The data are presented in Table III. In view of the recognized familial tendency to allergic manifestations these more complete data add significance to the limited data of Table II. Seventeen patients out of a total of 91 had at some time in their lives persistent urticaria. One more had psoriasis, and two others had had eczema.

The incidence of previous allergy is approximately the same among the males and females. There seems to be no predilection for a particular habitus.

PREVIOUS RHEUMATIC FEVER

The differentiation of arthritis, from early times to the present, has been represented by a succession of separations of the rheumatic arthropathies from the chronic arthropathies, to the final separation of atrophic arthritis from hypertrophic arthritis. There have seemed to be interrelations all along the line, so that even today differentiation is not at all easy in certain cases, even though the principle is conceded. Perhaps the best way to arrive at the truth is to study these various arthritic manifestations when they appear in the same individual. Certain members of this series had experienced in the past the symptoms and signs of rheumatic fever.

Seven males out of a total of 39 questioned had had rheumatic fever. Four females out of a total of 57 questioned had experienced rheumatic fever. The incidence of such a history is of less importance than the differentiation which the patient makes between the two epi-

TABLE II

NUMBER OF PATIENTS GIVING FAMILY HISTORY OF ALLERGY, OR ARTHRITIS, OR BOTH

	F. H. arthritis only	F. H. arthritis and allergy	F. H. allergy only	F. H. of neither
Allergy present in patient	8	3	1	4
Allergy not present in patient	20	1	2	

TABLE III

INCIDENCE OF PAST ALLERGIC HISTORY IN 91 PATIENTS

Females

	Asthenic		Intermediate		Sthenic	
Blond	No allergy	11 cases	No allergy	4 cases	No allergy	4 cases
	Urticaria	2 cases			Urticaria	2 cases
Intermediate Blond	No cases		No cases		No cases	
Brunet	No allergy	10 cases	No allergy	7 cases	No allergy	5 cases
	Inflammatory rheumatism	1 case	Urticaria	4 cases	Urticaria	1 case
					Psoriasis	1 case
					Urticaria and hay fever	1 case
Intermediate Brunet	No cases		No allergy	1 case	No allergy	1 case

Males

	Asthenic		Intermediate		Sthenic	
Blond	No allergy	4 cases	No allergy	2 cases	No allergy	1 case
	Urticaria	1 case	Urticaria	1 case	Urticaria and inflammatory rheumatism	1 case
	Eczema	1 case	Eczema	1 case		
	Acute g-c arthritis	1 case				
Intermediate Blond	No allergy	1 case	No allergy	1 case	No cases	
			Urticaria	1 case		
Brunet	No allergy	10 cases	No allergy	2 cases	No allergy	6 cases
	Urticaria	2 cases	Urticaria	1 case		
Intermediate Brunet	No cases		No cases		No cases	

TABLE IV

NUMBER OF PATIENTS GIVING PAST HISTORY OF ACUTE INFLAMMATORY ARTHRITIS OR ACUTE RHEUMATIC FEVER. FIGURES REPRESENT YEARS BY WHICH ACUTE ARTHRITIS PRECEDED ATROPHIC ARTHRITIS

Males	*Females*
7 patients gave positive history out of 39 questioned	4 patients gave positive history out of 57 questioned
4, 6, 8, 9, 11, 30, 36	1, 2, 12, 23

sodes. When these patients are questioned carefully in detail about the two diseases, there can be no doubt but that they are distinctive. The one is an acute condition which while painful is of minor consequence in the life of the subject, compared with the constant nagging and debilitating influences of the atrophic arthritic state. Pain and discomfort are proportional to signs in rheumatic fever, while in atrophic arthritis pain and debility are out of all proportion to signs. These patients were comparatively well individuals when they developed rheumatic fever; they were already sick individuals when they developed atrophic arthritis.

While they did not appear in any of the cases of this series, in a few other patients of the larger series of 612 cases, acute rheumatic manifestations (carditis, rheumatic pleural effusion, and erythema nodosum) supervened upon the atrophic arthritis. When rheumatic manifestations appeared, the atrophic arthritis became better rapidly. Occasionally allergic manifestations have supervened upon the atrophic arthritis, with benefit always to the latter. It is probably of significance that rheumatic fever so far as joint manifestations are concerned, has always preceded, by varying intervals, the onset of atrophic arthritis. For many years (see Jones[1]) there has been a suspicion that in some way the two diseases were related. As yet the relation has not been made clear. The observations noted above would suggest that the relation is a reciprocal one. The most likely explanation for this interesting observation is that both conditions depend upon constitutional reactibility, and that the two constitutional states are antagonistic. Observations which soon are to be mentioned will tend to define the constitutional state which determines atrophic arthritis. Upon such a foundation it becomes legitimate to build theories and propagate investigations of the relation of infection to the disease.

LOSS OF WEIGHT

There was noted in the history of 26 patients an appreciable loss of weight. The average loss was 32 pounds in an average time of 18.5 months. The greatest loss of weight was in a female who had Type 2a arthritis, the loss being 100 pounds in six months. Table V presents the individual losses.

It is inconceivable that a local disturbance of the joints would lead to such marked loss of weight in such an appreciable number of patients. The type of emaciation, which involves not only subcutaneous tissue, but also muscle and bone substance, indicates the profound general effects of the disease. It is not recorded in sufficient records to warrant tabulation, but it can be mentioned that this loss of weight begins sometimes long before signs of arthritis appear.

PRODROMAL PERIOD

Physicians of the past century were aware of a prodromal period in this disease, as is testified by their writings which have been reviewed by Jones[1]. The student of arthritis should not fail to read the chapter on "Premonitory Symptoms" by this author; it will give him a sound basis upon which to develop ideas of the disease. If present-day literature can be taken as a criterion, it would seem that this phase of the disease either has not been recognized or else is considered of little importance. Upon it the foundation of prevention of atrophic arthritis must rest. It is analogous to the incipient signs of pulmonary tuberculosis; and, strange enough, many of the prodromal signs of atrophic arthritis are identical with those of incipient tuberculosis, although the two diseases almost never occur in the same subject[5].

TABLE V

GIVING LOSS OF WEIGHT FROM TIME OF ONSET OF PRODROMAL SYMPTOMS TO TIME OF ADMISSION TO HOSPITAL

Males			*Females*		
Type	Pounds lost	During	Type	Pounds lost	During
2a	60	11 mos.	2a	23	12 mos.
2a	45	17 mos.	2b	20	6 mos.
2a	25	12 mos.	3a	60	3 mos.
5	25	12 mos.	2a	59	3 yrs.
2a	30	7 mos.	1	12	12 mos.
2b	20	6 mos.	2a	23	6 yrs.
2b	20	3 mos.	2b	30	5 mos.
2b	35	1½ mos.	2a	35	11 mos.
2a	17	4 yrs.	2b	40	2 yrs.
2a	20	2 mos.	2ab	25	5 yrs.
2b	30	5 mos.	2a	100	6 mos.
2a	100	6 yrs.	2a	18	5 mos.
			2a	40	12 mos.
			2a	22	24 mos.

It is well to indicate first the duration of these signs and symptoms, because it emphasizes the extreme insidiousness of the disease, as well as the ample opportunity for prevention. The records of 57 cases of the series supply these data. They are tabulated in Table VI. Over one-half of these patients presented signs or symptoms of the prodromal stage for a year or more before the onset of arthritis symptoms. The disease may begin abruptly, especially after an acute illness, physical trauma or exposure, or profound emotional strain, but usually it does not do so. It would seem that a few subjects are endowed with prodromal symptoms and signs from birth. The transition from hereditary constitutional traits to the true prodromal stage of the disease may be so gradual, or so obscured by these hereditary traits, that it may be impossible to determine the real inception of the

disease. A few patients of this type appear in this series.

It was thought that there might be a relation between the duration of prodromal symptoms and the habitus, but this does not appear, at least in this small series. Neither did a tabulation of duration of the prodromal stage to initial type of arthritis indicate any significant correlation. This emphasizes further the identity of the disease in the various sub-types which have been given.

Jones[1] has arbitrarily grouped premonitory symptoms and signs into three classes: (1) those referable to the vasomotor system, (2) those referable to the muscular system, and (3) those of the sensory system. These symptoms and signs have been tabulated in Table VII, and the frequency with which they have appeared in the present series of 57 cases is given opposite them.

It is curious that Jones does not mention the

TABLE VI

SHOWING DURATION OF PRODROMAL PERIOD IN VARIOUS PHYSICAL TYPES

Duration	*Males*			*Females*		
	Asthenic cases	Sthenic cases	Intermediate cases	Asthenic cases	Sthenic cases	Intermediate cases
1 wk.	1			1		1
2 wks.	1					
2 mos.			1			
3 mos.	1		2			
4 mos.	1			1	1	
5 mos.				1		
6 mos.	1			4		1
8 mos.	1					
1 yr.	1	1		3	1	2
2 yrs.		1	2	1	1	1
3 yrs.	1	1	1	1	1	1
5 yrs.	5					
6 yrs.					1	
7 yrs.						1
10 yrs.					2	
12 yrs.	1					
13 yrs.			1			
15 yrs.					1	
16 yrs.						1
20 yrs.						2
23 yrs.				1		
30 yrs.					1	
41 yrs.		1				

TABLE VII

FREQUENCY OF PRODROMAL SYMPTOMS AND SIGNS IN 51 PATIENTS OF THIS SERIES

SIGNS AND SYMPTOMS NOTED BY JONES

Vasomotor

Ischemic crises 9 cases
Cold, moist, cyanotic extremities 16 cases

Muscular

Cramps 9 cases
Weakness 1 case
Wasting 4 cases

Sensory

Numbness of extremities 8 cases
Tingling of extremities 9 cases
Bone soreness 2 cases
Neuralgic pains 9 cases
Muscle pains 11 cases
Hyperesthesia of skin and muscles 1 case

Neurologic

Increased tendon reflexes 0 observed

ADDITIONAL SIGNS AND SYMPTOMS NOT MENTIONED BY JONES

Vasomotor and Autonomic

Flatulence 2 cases
Constipation 11 cases
General pallor 9 cases
Cold, moist, pale extremities 15 cases
Palpitation 9 cases
Indigestion 1 case
Excessive perspiration 5 cases
Headaches 6 cases
Intermittent exophthalmos 2 cases
Intermittent swelling of thyroid 1 case

Muscular

Twitching 3 cases
Stiffness 6 cases

Sensory

Sensitive to cold 14 cases

Neurologic

Frequency (urinary) 5 cases

Subjective

Fatigue 39 cases
Nervousness 16 cases
General weakness 12 cases
General decline in health 2 cases
Nervous breakdown 1 case

Objective

Loss of weight 15 cases
Ecchymoses 2 cases
Scleroderma 1 case

most common of all of the premonitory symptoms, for practically every patient experiences it and it is one of the earliest to appear. It is a sense of constant fatigue combined with the necessity of driving oneself to perform the most trivial of duties. Along with this there is a marked tendency to fatigue abnormally at muscular work.

The next most common symptom is increased nervous irritability. The tendency to abnormal nervous fatigue is equally as great as the tendency to muscular fatigue. Unless the mind is diverted by something intensely interesting it is almost impossible for these subjects to sit in one position for more than a very few minutes without moving. The appetite becomes capricious; the gastro-intestinal tract develops indications of an increased irritability; the heart becomes irritable; there may appear intermittent periods of urinary frequency; in fact, many symptoms and signs are so individualized that were not the complete picture of the prodromal stage so typical of autonomic nervous system and vascular involvement it would be very difficult to recognize them as indications of an approaching syndrome. The tendency for gradual loss of weight during this period, the not infrequent occurrence of afternoon temperature, and the general asthenia make not a few of these individuals strong suspects for tuberculosis. Yet they do not have tuberculosis. Likewise, the loss of weight, increased nervousness, abnormal sweating, and tendency to eye signs suggest hyperthyroidism. But the latter differentiation is made easily because they have a normal metabolism, and rather than being sensitive to heat, they are extremely sensitive to cold.

A discussion of the meaning of the signs and symptoms of this prodromal period will be presented in another paper, but it is important to emphasize in passing that this phase of the disease will bear much study. A quotation from Jones[1] is particularly appropriate at this time: "We are, I am sure, too prone to look upon the joint swellings when they appear as a new departure, as a something which has descended upon the unhappy patient like a 'bolt from the blue', and, disregarding these premonitory symptoms, to lose our link with the past and join the cloud of witnesses who testify to the cryptic origin of so many cases of rheumatoid arthritis. My own conception of the disease is that it starts, so to speak, from a pathological groundwork of toxemia, of which the primary manifestations are these said premonitory symptoms, which in its presence proceed to display themselves."

THE INCEPTION OF JOINT SIGNS

Inflammatory rheumatism presents a rapid succession of symptoms and signs. In fact signs often precede symptoms. The patient may go to bed at night and awake with a swollen, inflamed, tender joint. Or he may develop a chill, which is followed rapidly by fever, general malaise, and then a rapidly swelling joint which becomes painful as it swells.

How different the situation is in atrophic arthritis! The patient may develop soreness which persists for weeks without the appearance of joint signs other than tenderness to pressure; or, swelling may develop very slowly as the soreness persists. Other patients may experience the most intense aching and pain with gradual or rapid stiffening of the joint with very little to be seen sometimes for even weeks. The ways in which arthritic symptoms may develop in atrophic arthritis are quite variable; hardly two cases will give the same story. Essentially, however, the manner in which the disease develops within the joints follows the sub-classification of the first paper[2]. The most important fact to be emphasized at this time is the relatively long average time between the inception of symptoms and the appearance of signs. This time was recorded in 21 male and 29 female patients. The average interval between symptoms and signs in the males was 322 days, and in the females 511 days. The individual cases are shown in Table VIII. It must be a very peculiar bacterium, if true, which can act locally in this way.

TABLE VIII

INTERVAL BETWEEN JOINT SYMPTOMS AND SIGNS IN 50 PATIENTS OF SERIES

Males Years	*Females* Years
	17.000
4.000	4.000
4.000	4.000
2.500	3.500
1.750	3.000
1.000	3.000
1.000	2.000
1.000	.500
.660	.500
.660	.500
.250	.500
.250	.500
.330	.330
.170	.330
.170	.100
.170	.100
.170	.100
.100	.100
.020	.100
.010	.040
.003	.020
.001	.010
	.010
Ave. 0.88	.010
	.010
	.0003
	0.0
	0.0
	0.0
	Ave. 1.4

TABLE IX

INCIDENCE OF BONE SYMPTOMS

	Males				*Females*			
	Aching		Soreness		Aching		Soreness	
	Type	Cases	Type	Cases	Type	Cases	Type	Cases
Not present	2a	17	2a	9	1	2	2a	5
	2b	12	2b	12	2a	20	4b	1
	2ab	1	2ab	1	2b	15	5	2
	5	1			2ab	1	1, 5	1
					4b	1		
					5	3		
					1, 5	1		
Mild	1	1	2a	3	2a	1	2a	1
			2b	1			2b	5
							2ab	1
Moderate	2a	2	2a	7	2a	3	1	2
	2b	3	2b	5	2b	3	2a	13
					2ab	1	2b	10
							2ab	1
Marked	2b	2	2a	1			2a	6
			2b	2			2b	3
			5	1			2ab	1
							5	1

TABLE X

LOCATION OF BONE ACHING

Location	Number of cases
Os Calcis	1
Humerus	3
Tibia	7
Femur	2
Pelvis	1
Scapula	3
Spine	1
General	1

TABLE XI

LOCATION OF BONE SORENESS

Location	Number of cases
Os Calcis	2
Tibia	42
Humerus	39
Spine	8
Feet	11
Femur	2
Wrists	1
General	8

TABLE XII

INCIDENCE OF MUSCLE SYMPTOMS, BOTH SEXES COMBINED

	Aching		Soreness		Stiffness		Weakness		Cramps		Twitching		Tremor	
	Type	Cases	Type	Cases	Type	Cases	Type	Cases	Type	Cases	Type	Cases	Type	Cases
None	1	2	1	2	1	1	1	2	1	1	1	1	1	2
pres-	2a	45	2a	37	2a	13	2a	19	2a	29	2a	36	2a	40
ent	2b	32	2b	22	2b	8	2b	16	2b	24	2b	21	2b	27
	2ab	4	2ab	1	4b	1	4b	1	2ab	1	2ab	3	2ab	3
	4b	1	4b	1			5	1	4b	1	4b	1	4b	1
	5	2					1, 5	1	5	2	5	3	5	3
	1, 5	1							1, 5	1	1, 5	1	1, 5	1
Total		87		63		23		40		59		66		77
Mild	2a	1	2a	3	1	1	2a	2						
					2a	7	2b	5						
					2b	10	5	1						
					2ab	2								
Moderate	2a	2	2a	6	2a	15	2a	7	2a	6	2a	3		
	2b	4	2b	8	2b	7	2b	6	2b	6	2b	7		
	5	1	2ab	2	5	1			2ab	2				
			5	3	1, 5	1			5	1				
			1, 5	1										
Severe	2b	1	2a	1	2a	17	2a	24	1	1	1	1	2a	5
			2b	1	2b	13	2b	10	2a	7	2a	3	2b	4
			2ab	1	2ab	2	2ab	3	2b	2	2b	4		
			5	1	5	2	5	2	5	1	5	1		
General	2a	1	2a	2										
			2b	5										

TABLE XIII

MUSCLE SYMPTOMS VS. MUSCLE SIGNS

Weakness present when denied		Weakness not present or mild when complained of strongly	
Males	Females	Males	Females
3	3	2	4

MUSCLE AND BONE SYMPTOMS AND SIGNS

We can now turn our attention to other symptoms and signs which refute the theory of local infection of the joints as the cause of the disease. They demonstrate further that the affection is not entirely "arthritic". Bone and muscle symptoms and signs are an equally prominent feature. Table IX gives the incidence of bone soreness and aching as distributed among the two sexes and the different initial types of arthritis. Table X gives the incidence of this symptom in different bones. Table XI gives the incidence of bone soreness in different bones. The protagonists of local infection must extend their theory to bones, as well as joints, if they can do so logically, for we find this common arthritic symptom and sign altogether too frequently involving the shaft of bone not to have it of significance.

Table XII discloses the frequency of muscle symptoms in this group of patients. Table XIII is given to indicate the very occasional occurrence of a discrepancy between symptoms and signs of muscle weakness. Three common muscle signs of atrophic arthritis are shown in Table XIV in relation to types of arthritis for both sexes. Twenty-one patients had marked general muscle atrophy; the distribution between types and sexes is shown in Table XV.

Tendon reflexes are increased in a high proportion of patients; Table XVI shows the distribution of this finding. This tends to reflect the general nervous irritability of the subjects of this disease, although there is a pronounced tendency for the tendon reflexes to be of unequal intensity throughout the body. As the disease progresses and muscle atrophy becomes more extensive, there is a gradual loss of tendon reflexes until they may disappear altogether.

It should be emphasized that such a simple explanation as disuse is not tenable as accounting for the muscle atrophy which is seen in atrophic arthritis. It may occur with great rapidity, and has a distinct tendency to symmetrical distribution. It not infrequently precedes joint involvement, and is not dissimilar at times to the course of muscle signs in anterior poliomyelitis. Atrophy of disuse is seen, of course, but it can be differentiated easily.

TABLE XIV

INCIDENCE OF MUSCLE SIGNS IN THE SEVERAL TYPES OF ATROPHIC ARTHRITIS
(Types as given are final types)

	Males						*Females*					
	Atrophy		Weakness		Tremor		Atrophy		Weakness		Tremor	
	Type	Cases	Type	Cases	Type	Cases	Type	Cases	Type	Cases	Type	Cases
None present	2a	9	2a	6	2a	17	2a	14	1	2	2a	30
	2b	9	2b	8	2b	17	2b	10	2a	9	2b	15
	5	2	5	2	2ab	1	4b	1	2b	7		
					5	2	5	2	4b	1		
							1, 5	1	5	1		
									1, 5	1		
Total		20		16		37		28		21		45
Slight	2a	2	2b	3			2a	3	2a	3		
	2b	1					2b	1	2b	3		
							2ab	1				
					Fine						Fine	
Moderate	2a	1	2a	6	2a	2	2a	7	2a	4		
	2b	2	2b	3			2b	1	2b	2		
							2ab	1				
					Coarse						Coarse	
Marked	2a	8	2a	7	2b	3	2a	9	2a	16	2a	3
	2b	8	2b	6			2b	6	2b	6	2b	3
	2ab	1	2ab	1			2ab	1	2ab	2		
									5	1		

TABLE XV

INCIDENCE OF GENERALIZED AND EXTREME MUSCLE ATROPHY

Males		*Females*	
Final Type	Cases	Final Type	Cases
2a	2	2a	8
2b	1	2b	8
2ab	1	2ab	1

JOINT SYMPTOMS AND SIGNS

The arthritic symptoms of this disease are well known. Their incidence will be found in Table XVII. They are of importance mainly in contrast to joint signs, which are given in Table XVIII. The symptoms appear to be out of all proportion to signs of inflammation. On the other hand, the number of patients who show evidence of joint destruction (ankylosis) indicates that there must be some good reason for the pronounced symptoms, even though this surely cannot be attributed to a primary inflammatory process. It is of particular interest to note that ankylosis occurred with much greater frequency in patients who at no time showed signs of inflammation than in those who did. Local fever and redness play an extremely minor rôle in the disease. The high incidence of crepitation upon motion of a joint is of considerable significance. It indicates a lack of synovial fluid, a roughening of the articular cartilages, and by inference, when considered in the light of other signs, a decreased circulation and fluid exchange in the synovial membrane.

TABLE XVI

TENDON REFLEXES IN RELATION TO FINAL TYPES OF ARTHRITIS

	Males		*Females*	
	Type	Cases	Type	Cases
Normal	2b	2	2a	2
			2b	2
			5	1
Slightly increased	2a	5	2a	9
	2b	2	2b	1
	2ab	1	2ab	1
Moderately increased	2a	7	2a	12
	2b	11	2b	4
	5	2	2ab	2
Markedly increased	2a	4	1	2
	2b	2	2a	8
			2b	11
			5	1
			1, 5	1

TABLE XVII

NUMBER OF CASES SHOWING VARIOUS JOINT SYMPTOMS

	Aching	Soreness	Stiffness	Crepitus	Pain on motion
Denied	23	8	5	85	4
Mild	29	19	19	17	10
Moderately severe	37	60	30		56
Markedly severe	10	13	48		29
Extremely severe	3	2			3

BLOOD PRESSURE

Atrophic arthritis has pronounced vascular manifestations,—so pronounced, in fact, that it may be regarded as a disease of the peripheral vascular system, being caused by a number of processes which lead to secondary vascular disturbances. When pathologic observations are used to illuminate the clinical findings, it is impossible to accept any other conclusion.

TABLE XVIII

INCIDENCE AND NATURE OF JOINT SIGNS

Swelling
- Slight in 36 cases
- Moderate in 33 cases

Local Fever
- Present in only 9 cases as follows:
  - Type 2a Slight in 4 cases
  - Type 3a Slight in 3 cases
  - Type 2b Slight in 1 case
  - Type 3a Moderate in 1 case

Local Redness
- Present in only 6 cases as follows:
  - Type 2a Cyanotic redness in 2 cases
  - Type 2b Cyanotic redness in 1 case
  - Type 3a True erythema in 2 cases
  - Type 3a Marked cyanotic redness in 1 case

Ankylosis
- Partial in 34 cases as follows:
  - Type 2a 9 cases
  - Type 2b 20 cases
  - Type 2ab 1 case
  - Type 3a 3 cases
  - Type 4b 1 case
- Complete in 7 cases as follows:
  - Type 2a 1 case
  - Type 2b 4 cases
  - Type 3a 1 case
  - Type 4a 1 case

Crepitus found at examination
- Knees only 47 cases
- Other joints only 2 cases
- Knees and other joints 24 cases

TABLE XIX

BLOOD PRESSURE, AVERAGE RESTING PULSE RATE, CORRELATED WITH AGE, SEX, PHYSICAL HABITUS, AND ACTIVITY

A = Asthenic. I = Intermediate. S = Sthenic.
— — Very little activity.
— Activity considerably restricted.
— + Up and about but limited activity.
+ Fairly normal activity but fatigues easily.
+ + Full normal activity.

Age Group	Male				Female			
15-19	I	— +	120/78	86	A	—	128/82	92
	A	— +		80				
	I	— +		85				
20-29	A	— +	115/65	80	A	—	120/80	88
	A	— +	110/65	88	I	+	115/70	80
	A	— +	112/78		A	+	120/60	80
	A	—	104/54	115	A	— —	90/60	90
	A	— +		80	A	— —	88/65	90
	A	+	118/70	94	A	—	132/88	94
	A	— +	132/80		A	—	135/95	86
					A	+		80
					I	— +	96/60	88
					A	—	90/70	95
					I	—	120/85	90
					I	—	120/76	90
					I	—	110/68	86
					I	— +		90
					I	+	140/70	74
					S	+	116/80	80

30-39	I	—	125/75	90	A	—	120/76	90
	A	—+	118/58	80	A	——	105/70	90
	A	—	135/75	85	A	—+	120/80	104
	I	—+	128/85	85	S	—	120/80	86
	A	—+		82	I	—	90/60	70
	S	—+	130/84	88	S	—		85
	S	—+	138/80	90	S	—	100/72	92
	A	—	120/80	88	A	——	100/55	110
	I	—		94	A	—	134/84	
					S	—	120/80	
40-49	A	——	80/50	90	A	——	136/88	92
	S	—+	120/74	80	S	—	140/100	
	I	—	96/70	90	I	—+	140/80	88
	S	—+	140/100	76	S	—+	124/70	78
	I	—	104/74	80	A	——	94/76	92
	I	——	125/85	85	I	——	142/95	100
	A	—	140/80		A	—	102/68	80
	A	—	100/60	90	I	—	130/85	86
	S	——		80	A	——	100/80	98
	S	—+		74				
	A	—		90				
50-59	A	—	110/75	80	A	——	148/85	90
	I	—+	120/72	80	A	——	170/110	88
	I	+	130/80	80	S	——	190/110	110
	S	—+		66	S	—	130/90	80
					A	—	150/88	90
					I	—	180/80	
					A	—	140/80	88
					A	—	120/80	78
					I	—	134/62	75
					I	—		90
					A	——		80
					S	—+	180/80	88
					S	—		84
60-69	I	—	98/76		S	——	220/110	85
					A	——	165/92	95
					I	—+	130/70	
70-79	I	—	125/70	80				

In view of this conclusion it is of interest to examine the blood pressure findings in these patients. The values which are reported in Table XIX and Charts I and II were obtained after the patient had reclined for ten minutes and not until successive determinations gave a constant value. The sexes have been separated, the habitus of the subject is given, the degree of physical activity is recorded, and the average resting pulse rate has been taken from the temperature chart.

Nearly every patient presents an abnormality in blood pressure. The various combinations of abnormal elevation or lowering of systolic and diastolic pressures are easily detected in the charts. There is evidence of an attempt on the part of the vascular system to maintain adequate pulse pressure either through lowering of the diastolic or elevation of the systolic pressure. The intricacies of this adjustment and their significance are hardly susceptible to plausible explanation. The level of physical activity appears to bear no relation to the level of the blood pressure since most of the patients exhibited a pronounced decrease in activity. Neither is there any apparent correlation between level of blood pressure and the habitus of the subject, aside from the fact that hypotension does not appear in a single sthenic subject.

Of greater importance is the relation of change in blood pressure to improvement of arthritis under therapy. It can be mentioned only that as the arthritis improves, the hypertensive subjects have a lowering of their blood pressure, particularly the diastolic; and hypotensive subjects have an elevation of systolic and lowering of diastolic pressures. The blood pressure is, therefore, of considerable importance in indicating therapeutic effects of different

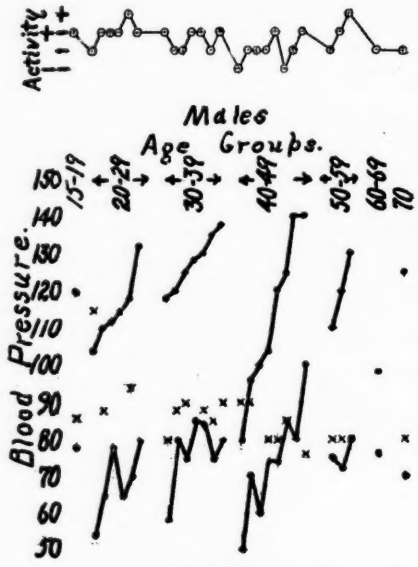

CHART I.
Blood Pressure, Pulse Rate, and Activity of Males by Age Groups.

⊙ Activity. ● Diastolic and Systolic Pressures. X Pulse Rate.

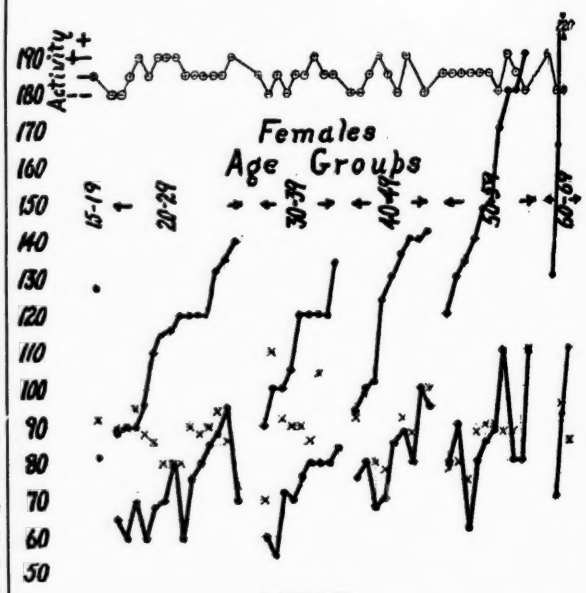

CHART II.
Blood Pressure, Pulse Rate, and Activity of Females by Age Groups.

⊙ Activity. ● Diastolic and Systolic Pressures. X Pulse Rate.

forms of treatment. Moreover, these therapeutic changes serve to emphasize further the abnormality of the blood pressure in this disease. Why both hypertension and hypotension are characteristic of the disease is a question of very great interest and significance, but it cannot be discussed at this time.

THE CONSTITUTIONAL SYMPTOMS AND SIGNS OF ATROPHIC ARTHRITIS

There is no real differentiation between the constitutional signs and symptoms of the prodromal stage of atrophic arthritis and those of the arthritic stage. These only become more pronounced as the arthritic stage appears. Signs and symptoms which may not have appeared in the prodromal stage may be added to those which have been present before arthritic symptoms developed. This definite continuity of the constitutional manifestations of the disease throughout both stages is additional evidence that the disease is secondarily rather than primarily arthritic.

Cold extremities were noted in 74 of the patients in this series; 33 of them males and 41 females. The distribution among types is as follows:

	Males	Females
2a	17 cases	20 cases
2b	13	15
2a, 2b	1	3
5	2	1
1	0	2

This observation was made under conditions in which the hands of normal persons were warm.

Cyanosis of the finger or toe nails was noted in 27 patients; 14 males and 13 females, distributed among types as follows:

	Males	Females
2a	5 cases	6 cases
2b	7	7
5	2	0

Ischemic finger or toe nails occurred in 31 patients; 15 males and 16 females, distributed among types as follows:

	Males	Females
2a	9 cases	9 cases
2b	6	6
1	0	1

Repeated observations of the same patient may disclose ischemic nails at one time and cyanotic nails at another. The above observations were made upon admission.

Purpuric areas may occur under the skin spontaneously in subjects of atrophic arthritis. It was noted in only two females of this series and has been seen with about the same frequency in the total series of 612 cases. These areas may appear quite suddenly without previous injury, and their most frequent site is the extensor surfaces of the lower legs. They are apt to be initiated with a sudden stinging sensation in the region where the spot is to appear. They recur repeatedly and are not related to venous varicosities. The types of cases in which it was noted in this series were 2a, 2b and 2a, respectively.

Not only do these patients occasionally show spontaneous purpuric areas, but with greater frequency they complain of the formation of "black and blue" spots after slight injury.

Ischemic crises occur with probably greater frequency than was noted in this series. Unobserving patients would entirely miss this sign. Sometimes these crises are associated with symptoms of numbness and tingling and other times not. They are likely to appear when the patient is exposed to chilling or when under emotional stress. The blanching of the skin may involve a single finger or toe, several digits, or an entire hand or arm. Ten patients complained of this vascular manifestation. The distribution among types is as follows:

	Males	Females
2a	2 cases	4 cases
2b	1	2
5	0	1

Claudication was experienced by only one patient; male, type 5. This involved the calf muscles. The symptom was noted several times in the larger series of cases, and would probably have been complained of with greater frequency had not the activities of these patients been so limited by joint disability.

Anginoid attacks were experienced by one patient of the series. The patient was a 40-year-old male with type 5 arthritis. He was observed in one of these attacks which appeared to be precipitated by looking out at fresh snow which reflected strongly the rays of a very bright sun. The attack commenced with palpitation (the heart rate was 140), and then the patient experienced blurring of vision, nausea, great weakness, epigastric pain, and precordial pain which radiated down the left arm. The left hand was cold and pale, the abdomen tympanitic, the heart regular, and the pupils widely dilated. The pupils would not react to bright light or accommodation for several days even though the tachycardia and other symptoms subsided within a few hours.

Susceptibility to blushing or paling is noted in the records of four patients; two males, both Type 2b, and two females, both Type 2a.

Sclerosed radial arteries were noted in three patients; two males, both Type 2b, one 36 years of age and the other 72 years, and in one female with Type 2a arthritis, age 68 years. Palpable radial vessels were noted with much greater frequency in succeeding cases of the total series of 612 since attention was not drawn to this finding

until late in the study. Sclerosing arteritis would appear to be a common characteristic of the disease as it advances, regardless of age.

Fainting attacks of disturbing frequency appeared in two patients of this series; one a male, Type 2a, the other a female, Type 2b.

General pallor was present in 31 patients; 15 males and 16 females. The distribution among types is as follows:

	Males	Females
2a	6 cases	8 cases
2b	8	5
2a, 2b	0	2
1	0	1
5	1	0

Pallor was not found to be related to anemia.

Chilliness to an abnormal degree was complained of in six instances as recorded in the histories. It is probable that the question was not asked in many other instances, as this is a very common symptom. The cases are distributed as follows:

	Males	Females
2a	0 cases	1 cases
2b	1	1
2a, 2b	0	2
1	0	0

Recurring erythematous patches on the skin was complained of by one patient, a female with Type 2a, 2b arthritis. This sign was noted in other cases of the larger series. It appears to be due to areas of dilated capillaries in which stasis occurs, since it is not associated with extravasation of fluid and does not persist. It is possible that such disturbances may precede the formation of the petechial areas mentioned above.

The signs and symptoms which have been given above are manifestations of the vascular phase of the disease. The distribution among cases is not so striking as it actually is when individual cases are examined thoroughly. This was not done in many of the cases of this series because much of the available time was necessarily devoted to treatment. The data which have been presented, however, are sufficient to emphasize the presence of important signs in this disease other than those which can be classified as arthritic.

Numbness and tingling coming in paroxysmal attacks were noted in the histories of 18 patients; 7 males and 11 females, distributed among types as follows:

	Males	Females
2a	4 cases	5 cases
2b	3	4
5	0	1
1, 5	0	1

This is probably a vascular manifestation although it is a sensory symptom, due to the probability that ischemic crises about sensory nerve endings lead to this type of nerve stimulation.

Exophthalmos was noted in 3 males and 8 females, distributed among types as follows:

	Males	Females
2a	1 case	2 cases
2b	2 cases	6

One female of Type 2b had intermittent, unilateral exophthalmos; another female of Type 2b had bilateral, intermittent exophthalmos. This was observed personally by the author, and was very pronounced.

Intermittent swelling of the thyroid was noted in one female patient with Type 2b arthritis. This recurred repeatedly at weekly intervals, coming on at the end of the week, when the patient was fatigued from work, persisting over Sunday, and subsiding on Monday and Tuesday. Several times it was observed that one side of the thyroid subsided on Monday and the other side on Tuesday. It might also be mentioned, in order to show the extreme reactibility of this subject, that whenever she changed her supply of drinking water, she developed urticaria, during which periods she was free from arthritis, and felt unusually vigorous.

Moist extremities were observed and recorded in 33 males and 36 females, distributed among types as follows:

	Males	Females
2a	17 cases	18 cases
2b	13	13
2a, 2b	1	3
5	2	1
1	0	1

The degree of moisture of the palms and soles was observed to vary inversely with the coldness of the extremity. The amount of perspiration in some of the cases was so great that drops of water could be brushed from the patients' palms, and many complained that it seriously interfered with writing or sewing. One patient showed the author a sewing needle which had become badly rusted and tarnished from the previous day's use.

Excessive perspiration on physical exertion or nervous excitement was complained of by 8 male and 4 female patients, distributed among types as follows:

	Males	Females
2a	5 cases	0 cases
2b	3	2
2a, 2b	0	1
5	0	1

Abnormally dilated pupils were noted in 2 males and 4 females.

	Males	Females
2a	1 case	0 cases
2b	0	3
2a, 2b	0	1
5	1	0

Palpitation upon exertion or nervous excitement was experienced by 7 males and 20 females.

	Males	Females
2a	7 cases	9 cases
2b	3	3
2a, 2b	0	2
1	0	2
5	0	1

Tympany over the large bowel to a marked degree was found in 2 males and 3 females. The males were Type 2b; the females, respectively, Types 2a, 2b, and 2a, 2b. Fletcher[6] has noted on barium enema examination a distended colon as a common roentgenologic finding in the disease. The above figures are obviously incomplete as it has been a most common observation in the author's experience.

The series of symptoms and signs which have just been recorded are indicative of a disturbance in balance of the autonomic nervous system, with manifestations of an increased relative tone of the sympathetic division. While the figures are incomplete, it can be seen readily that these symptoms and signs are common to the different types of atrophic arthritis.

Easy fatigability was recorded in the histories of only 6 males and 10 females, distributed as follows:

	Males	Females
2a	4 cases	5 cases
2b	1	4
2a, 2b	0	1
5	1	0

Practically every arthritic has this complaint. It does not appear frequently in this series probably because the question was not asked in the routine history from which the data for the arthritic stage of the disease have been taken.

Abnormal nervousness is also a complaint which has a high incidence, but it is recorded in the histories of only 6 patients, all of them females, equally divided between Types 2a and 2b. This low incidence is again due to incomplete history taking. However, arthritics frequently deny, when questioned, any nervous instability, although their relatives and friends will testify to it, and it rarely fails to become evident when these patients are observed in their homes or on the ward. There is frequently a strong tendency to weep on the slightest suggestion; and they respond to strongly positive encouragement as a plant does to water. They are almost invariably unstable individuals, emotionally and nervously.

A series of miscellaneous but significant signs and symptoms are found in addition to all those which have been mentioned. Increasing *brittleness of the nails* is noted frequently, but it is recorded only in one Type 2b male, one Type 2a, 2b female, and a Type 5 female. *Dryness of the skin* was observed in one Type 2b male, one Type 2a female, one Type 1 female, and one Type 2a, 2b female. *Dryness of the hair* was complained of by one Type 2b male. *Atrophic skin* was noted in five females of Types 1, 5, 2a, 2a, and 2a, respectively.

The above atrophic changes are observed in extreme form occasionally. One of the author's patients has been reported by Gordon[7] as a case of scleroderma. Another patient of this series lost the sight of both eyes by corneal scarring; the blood Kahn test was negative, and there was no history to suggest syphilis. The author has seen two other patients with the sight of one eye lost through the same process. Another patient lost all of his hair, and repeatedly lost his finger and toe nails. Raynaud's paroxysms are seen occasionally in subjects of atrophic arthritis.

Chronic constipation was present in 31 patients of this series. The distribution among types is as follows:

	Males	Females
2a	6 cases	7 cases
2b	8	5
2a, 2b	0	3
5	1	1

The duration of constipation varied from 4 months to 30 years; it had always been present in 2 cases; it preceded the arthritis in most of the patients; and came on at the time of arthritis in 3 others. The average duration for the entire group was 9.9 years. Two of the group had hemorrhoids. Two other patients who denied constipation had hemorrhoids.

Six patients complained of idiopathic diarrhea. Each attack of diarrhea preceded an exacerbation of arthritis. One patient had urticaria with each attack of diarrhea, the arthritic exacerbation occurring when the diarrhea and urticaria subsided.

Headaches of unusual frequency and severity were complained of by 26 patients. The distribution among types follows:

	Males	Females
2a	3 cases	7 cases
2b	5	6
2a, 2b	0	2
5	1	1
1, 5	0	1

Headaches were either frontal or occipital, or both. They appeared to bear a relation to exacerbations of arthritic symptoms and to weather changes.

Two patients complained of transitory attacks of *vertigo*. Eight more patients complained of occasional dull frontal or occipital headaches.

Eye manifestations were present in 23 patients. One Type 2a male had occasional diplopia. Four patients had marked neuroretinitis, distributed as follows: male Type 2a, two females Type 2a, male Type 2b, and female Type 2a, 2b. One male Type 2a and one fe-

male Type 2b had frequent attacks of iritis. Another male Type 2b had severe iritis while in the hospital. One female mentioned above, Type 2a, aged 20 years, had corneal scars and vitreous sclerosis, with blindness coming on at the age of 7 years when the arthritis developed; the Wassermann reaction was negative. Another female, aged 30 years, Type 2a, complained of marked aching in the eyeballs, had arteriosclerosis of the retina, and pronounced papilledema without other signs of intracranial tension. A male Type 2b had slightly hyperemic optic discs, increased lachrymation, and complained of lid twitching. A male Type 5, mentioned in connection with anginoid attacks, complained of frequent aching of the eyeballs, and had fixed pupillary dilatation during the anginoid attack in which he was observed. A female Type 2a complained of marked eye fatigue after the onset of her arthritis. Another female Type 2b complained of attacks of blurring of vision and aching of the eyeballs. Two males, Types 2a and 2b respectively, complained of frequent attacks of aching in the eyeballs. Likewise, four females all of Type 2b, had the same complaint; in one it was unilateral. One female Type 2a had ptosis of the right eyelid with weather changes which affected her arthritis.

All of the above changes are referable to either vascular changes, autonomic system imbalance, or muscle changes.

Genito-urinary symptoms were noted with greater frequency than genito-urinary signs. Only two patients, both males, showed albumin in the urine. Nocturia of a significant type was present in eight patients. Only one of these was under 40 years of age. The urine was negative on examination in these patients. Frequency affected seven patients. This is an interesting complaint because its incidence was about the same in the larger group of 612 patients. It cannot be accounted for on the basis of urinary infection. It occurs only in the daytime, and is likely to be intermittent. It may usher in an exacerbation of the disease. It probably denotes increased nervous irritability.

One patient, aged 26 years, had very scanty menstruation with marked dysmenorrhea. As a group, dysmenorrhea is an unusual complaint. A more usual complaint is leucorrhea. The author believes that it is in the nature of a chronic catarrh. When these patients are seen in the gynecology clinic, they are reported as having chronic endocervicitis. It is the author's opinion that it is not to be explained on the basis of infection, and that it has very little, if anything, to do with the cause of the disease. It appears to be more in the nature of a manifestation of the disease.

CONCLUSIONS

The observations which have been reported in this paper serve to emphasize the more significant features of atrophic arthritis. It is unfortunate that the series of cases is small and the data not complete for an accurate statistical presentation. But the data are sufficiently extensive to compel serious consideration. They are also sufficient upon which to build a preliminary concept of the disease, and from which to define its physiologic characteristics.

It can be accepted, from this and the data of other investigators, that the disease has strong familial tendencies. What is inheritable about the condition can be arrived at only through a knowledge of the constitutional characteristics presented by its subjects. The incomplete data upon the allergic trait would suggest, at least, that an abnormal reactibility is common to a significant number of these patients. The strong familial disposition to the allergic state is well known. Possibly it is upon this bridge that the gap between arthritis in different members of the same family can be spanned.

However, allergy does not seem to be a prerequisite to atrophic arthritis; in fact, it seems to be its antithesis. This paradoxical situation can be explained only when the constitutional manifestations of atrophic arthritis are examined carefully. Allergic manifestations are evidences of a peculiar reactibility on the part of the autonomic nervous system, the vascular system and the smooth muscle system. Since atrophic arthritis is found in a fair proportion of subjects who previously have shown allergic disturbances, it would not be surprising if the constitutional manifestations of atrophic arthritis involved the three systems just mentioned. Strikingly enough, it is these very systems that appear to be involved, as a study of the prodromal symptoms and signs, and the constitutional symptoms and signs after the disease has become arthritic, will reveal. But in contrast to allergy, in which there is peripheral vascular dilatation, smooth muscle constriction (intestines and bronchi), and a slow pulse, we find in atrophic arthritis a rapid heart, an atonic bowel, and peripheral vasoconstriction. In other words, there appears to be in the allergic state an autonomic imbalance in favor of the parasympathetic division, and an imbalance in favor of the sympathetic division in the atrophic arthritis state. The two states are incompatible in the same tissue at a given time, so that now we have an explanation for the reciprocal relation of allergy to the disease. Furthermore, we have an explanation for the failure of antirheumatic therapy in atrophic arthritis, and finally, there is opened up a field for therapy whose indications have not been suspected before.

This is just the beginning of the study of atrophic arthritis, but it is a fair and logical beginning. A better appreciation in the past of the aspects of the disease which have been mentioned in this paper, and long ago by Jones[1], would have led, possibly, to more advance in this field than exists today. The extreme disinterest in the disease which has existed for so long, with the exception of a bare handful of earnest workers, will be corrected rapidly, as soon as the profound physiologic implications are more generally appreciated. It should be thought of as vascular disease, or neurovascular disease, and certainly not as "infectious arthritis".

SUMMARY

A series of 102 atrophic arthritic subjects has been examined from the standpoint of constitutional abnormalities, and the incidence of these manifestations has been presented.

It has been pointed out that these manifestations are referable to a disturbance of three common systems of the body, namely, the autonomic nervous system, the vascular system, and the smooth musculature.

Since the disease has its inception almost regularly in a prodromal period which is not arthritic, and since the constitutional signs of this period are so characteristic and prevail and become exacerbated in the arthritic stage, it would appear that the arthritic manifestations are of no more fundamental importance than the constitutional manifestations.

The constitutional aberrations in the states of atrophic arthritis and rheumatic fever have been discussed briefly, and the inference that they have a reciprocal relation has been drawn.

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MODERN LABORATORY METHODS FOR THE EARLY DIAGNOSIS OF PREGNANCY*

BY MAX DAVIS, M.D.,† AND ELISABETH W. WALKER, M.A.†

INTRODUCTION

THE early diagnosis of pregnancy has until recently been a very difficult problem. It is frequently of great interest and importance to both patient and physician to determine the existence or absence of a pregnancy at as early a period as possible. Pulmonary tuberculosis, primary and severe secondary anemias, glandular insufficiency, functional amenorrhea, psychoses, all may frequently cause difficulty in diagnosis. The physiologic amenorrhea of lactation and the early menopause throw many a patient into a nervous state of anxiety. The differential diagnosis between acute salpingitis and ectopic gestation, between pregnancy and uterine fibroid or ovarian cyst, and between complete and incomplete abortion, often taxes the skill of the most experienced gynecologist. The so-called "presumptive signs" of pregnancy may lead one to suspect the condition, but very often a reëxamination at a later date is necessary before a definite diagnosis can be made. This delay in diagnosis leads to a loss of valuable time to patients in whom pregnancy is contraindicated, and to a period of nervousness and uncertainty in women whose plans might be entirely changed, were they pregnant. For these reasons, many attempts have been made to develop dependable tests which would give this valuable information at a time when the ordinary clinical diagnostic methods could not furnish proof positive of pregnancy.

The phenomena of pregnancy are so complicated, and its effects upon the bodily mechanism are so profound even under normal conditions, that there occurs a multiplicity of physiologic and functional variations from the accepted normal non-pregnant state. The diagnostic significance of any one of these variations, however, depends upon its constant and regular presence, at an early stage, in all pregnancies, and its consistent absence in all other conditions. The various laboratory methods for diagnosing pregnancy depend upon these functional variations from the normal, and thus, with the intent of discovering these variations, a great multitude of tests have been elaborated. These tests all fall into one of three groups‡: *the metabolic,* such as the alimentary glycosuria and acetonuria tests; *the biologic,* represented by the Abderhalden reaction, the ninhydrin flocculation test, and the Aschheim-Zondek test; and *the chemical,* such as the bromine and hematoma tests. The majority of these tests for early pregnancy, however, have not stood the trial of time, since

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‡For a concise discussion of some of these tests, see article by Mathieu[1].

they have failed to pass one or more of the following criteria of a test valuable to the practicing physician: (1) Is it simple? (2) Is it delicate? (3) Is it accurate? As a result, there are very few tests which are still in use in most laboratories.

We shall now devote ourselves to a more detailed discussion of those reactions which have been and are still being considered in the recent literature. Their value has also been impugned and their accuracy has been the subject of much controversy. The only one of these tests which seems best to have withstood all criticism is the Aschheim-Zondek reaction, which will be the last to be discussed.

REVIEW OF PREGNANCY TESTS OTHER THAN THE ASCHHEIM-ZONDEK TEST

DIENST REACTION. In 1928, Dienst[2] reported a test for the early diagnosis of pregnancy, based presumably upon the increase of antithrombin in the serum and in the urine of pregnant women. He reported it to be very accurate. Narimatsu[3], using Dienst's technic for the urine, secured the following results: of 106 pregnant cases, 73 (68.8 per cent.) were positive, and 33 (31.2 per cent.) were negative. Of 50 non-pregnant cases, 17 (34 per cent.) were positive, and 33 (66 per cent.) were negative. According to Gragert and Zander[4], this test, because of its low percentage of accuracy, has proved to be of little value. They obtained a correct diagnosis in only five per cent. of the early pregnancies, and in only 13.8 per cent. of all pregnancies.

MANOILOFF REACTION. The publication of this test on the blood serum has evoked a series of both favorable and unfavorable reports. Manoiloff himself tested 696 sera with an average of 94 per cent. correct findings[5]. Of other investigators[6, 7] some claim an accuracy varying from 79 per cent. to 93 per cent.*; others an accuracy of 61 per cent. in the late months of pregnancy, with regularly negative results in the early months of pregnancy. Rodecurt and Jernakoff[8] declare that they have found it wholly unserviceable, the main difficulty lying in the interpretation of the many color tones, resulting from the test, either as distinctly positive or negative.

The present status of this test seems to be best summarized by the following conclusions[9]: (1) The Manoiloff reaction falls into the group of non-specific pregnancy tests. (2) It is of practically no value for the early diagnosis of pregnancy, and of only little value from the fourth month onward. (3) The reaction seems to increase with the advance of pregnancy. (4) In neoplasms, it is positive in two-thirds of the cases and negative in one-third. (5) The serum of patients suffering from gynecologic diseases is generally negative, except in those with neoplasms.

BERCOVITZ TEST. This test is one of the simplest yet described for the diagnosis of pregnancy. Because of its comparatively recent description (1930), it has as yet but a small literature, hence its accuracy cannot be definitely established. The technic is to mix one drop of 10 per cent. sodium citrate solution with five drops of the patient's blood and to instill this mixture into the patient's right eye, the left eye being used as a control. The reaction which indicates pregnancy is either a dilatation or contraction of the right pupil as compared with the control. Bercovitz[10] reported a series in which 96 out of 98 non-pregnant women were negative, and 60 out of 68 pregnant women were positive. Gordon and Emmer[11] report 90 cases with 100 per cent. accuracy in all the non-pregnant patients, but with several false negatives in the pregnant patients, without, however, quoting actual statistics as to the percentage error. This series is too small and does not contain enough cases of early pregnancy to give a definite conclusion as to the true value of the test.

NINHYDRIN FLOCCULATION TEST†. Like the Manoiloff reaction, this test on the blood serum has also had many protagonists and antagonists. Our personal experience with this test consists of over 1200 cases, in which it has shown an accuracy of approximately 96 per cent. in the non-pregnant cases and of 93 per cent. in the pregnant cases. Patients with pelvic inflammatory or neoplastic conditions, however, give correct results in only about 80 per cent. of the cases, thus taking away a great deal of the value of a positive test in the differential diagnosis of such conditions from pregnancy. This test becomes positive within the first ten days after the missed period. Its chief advantages are the simplicity of its technic and the rapidity with which a report can be given to the patient. The advantage of speed, however, has been lost somewhat since the development of a modification of the Aschheim-Zondek test, which enables a report to be given in about thirty hours. We have checked the Ninhydrin Flocculation test against the Aschheim-Zondek reaction, and have found the latter to be more satisfactory. (See Table VIII.)

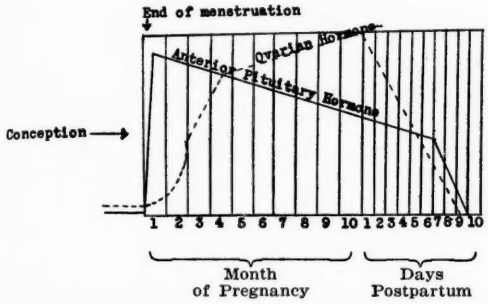
FEMALE SEX HORMONE TESTS. Three different technics have been developed on the basis of the female sex hormone as a test for pregnancy, namely, those of Frank and Goldberger, of Siddall, and of Mazar and Hoffman. It is now known that during the menstrual cycle there are changes in the quantity of female sex hor-

*Brovkin[6] reports 90 per cent. accurate in 215 pregnant cases, 83 per cent. accurate in 98 healthy non-pregnant women, 79 per cent. accurate in 43 unhealthy (suffering from pelvic inflammation, fibroids, or cysts, and after miscarriage) non-pregnant cases.

†For a detailed discussion of the test, with references to the literature, see article by Davis[12].

mone circulating in the blood of the normal woman[13]. In the first part of the cycle, there is very little hormone in the blood, but it gradually increases in quantity, reaching a maximum in the premenstrual phase. The hormone level in the circulation is low immediately after conception and until the seventh week of pregnancy, after which it rises rapidly, remaining high until the onset of labor.

DIAGRAM OF AMOUNT OF OESTRIN (FEMALE SEX HORMONE) AND ANTERIOR PITUITARY SUBSTANCE IN THE URINE OF PREGNANT WOMEN
(After Aschheim and Zondek[14])


End of menstruation
Ovarian Hormone
Anterior Pituitary Hormone
Conception
1 2 3 4 5 6 7 8 9 10 1 2 3 4 5 6 7 8 9 10
Month of Pregnancy
Days Postpartum

OESTRIN AND ANTERIOR PITUITARY HORMONE IN URINE OF PREGNANT WOMEN
(After Aschheim and Zondek[14])

Stage	Oestrin m. u. per liter	Ant. Pit. Hormone m. u. per liter
1-8 weeks	300- 600	3000-5000
3-7 months	5000- 7000	3000-6000
7-10 months	6000-10000	2000-3000

Dohrn and Faure[15] demonstrated large quantities of this hormone in the urine and feces of pregnant women. "These discoveries revealed two outstanding facts pertaining to the subject under discussion: namely, that the corpus luteum of pregnancy and later the placenta produce large quantities of female sex hormone to stimulate the vascularization and growth of the uterus, and that the difference between the amount sufficient for physiologic needs and the amount produced is eliminated by the kidneys and intestines. Another fact worth noting is the meager quantity of female sex hormone in the circulating blood during the preplacentation period of pregnancy, when growth of the uterus is relatively slow, as compared with the quantities of this hormone eliminated through the urine and feces. What is the object of nature in thus depleting the blood of female sex hormone during early pregnancy? Papanicolau[16], Corner and Allen[17], and others indirectly answered this question when they produced experimental proof that the corpus luteum produces also an inhibitory hormone which prepares the endometrium for nidation and gestation*. Repeated injections of this lutein hormone are capable of suppressing ovulation and estrus in the guinea pig indefinitely. It is essential, at least, during the preplacentation period of pregnancy, when its removal is usually followed by abortion"[19].

Upon this basis, Frank and Goldberger developed their technic for the diagnosis of pregnancy, which is performed essentially by securing the hormone from 40 c.c. of blood, injecting it into a castrated mouse, and interpreting the results by means of vaginal spreads†. They did not give any statistical report upon their cases of pregnancy[22].

The Siddall[23] test depends upon the effect of anterior pituitary lobe hormone* as well as upon the effect of the female sex hormone in the blood serum of pregnant women on the genital tract of immature mice. One cubic centimeter of blood serum is injected daily for five days into an immature mouse. At the end of that period, the total mouse weight divided by the weight of the uterus with the ovaries attached gives a ration of 400 or less, if the woman is pregnant. Siddall reported 139 cases with an error in only six cases. Mazar and Hoffman[19], on using this test, found that 76 per cent. of 150 pregnant cases gave a positive reaction, and 83 per cent. of 164 non-pregnant cases gave negative results.

The fact that both these tests depend upon the presence of female sex hormone in the blood indicates the reason for the lowered percentage of correct results in positive cases, for, as we have seen, the female sex hormone is not contained in large quantities in the blood early in pregnancy. (See chart and table on this page.) Therefore, instead of using the blood as the source for the female sex hormone, Mazer and Hoffman[24] developed a technic wherein they used the urine, which they injected into castrated white mice. In their first paper, these authors report 61 positive results out of 67 pregnant cases, and 127 negative results out of 142 non-pregnant patients. In their second report, 112 (75 per cent.) of 150 pregnant women gave positive results, and 158 (96 per cent.) of 164 non-pregnant patients gave negative results. The accuracy in the pregnant cases is somewhat low by this method. Furthermore, the claimed advantage of ease of performance loses some of its value because the Friedman modification of the Aschheim-Zondek test, to be described, in addition to greater accuracy, has an even simpler technic. There is also, in performing this test, an admitted difficulty of interpretation of the results by the smear method.

PITUITARY HORMONE TESTS INCLUDING THE ASCHHEIM-ZONDEK TEST

It has long been known that there is an interrelationship between the pituitary gland and the genital organs, but it is only within the last

*For an interesting discussion of this balance of the female sex hormone and the corpus luteum during pregnancy, see article by Kelly[18].

†The method of reading by means of vaginal spreads was worked out by Stockard and Papanicolau[20] and checked by Allen[21].

*See below, *Pituitary Hormone Tests.*

few years that some understanding of this relationship has been gained. By the transplanting of anterior pituitary glands into sexually immature female animals or into older animals from which the anterior pituitary had been removed, Smith[25] and Engle[26] were able to produce sexual maturity, that is, ovulation and corpora lutea formation with consequent estrus. Zondek and Aschheim[27] arrived at the same results, and they concluded that, "The anterior lobe hormone is the primary, and the ovarian hormone is the secondary. The anterior lobe hormone brings the follicular apparatus into action, fires off the follicular ripening, and mobilizes the secondary ovarian hormone in the follicular cells. This, then, acts in a specific way on the uterus and vagina." It had also been known that the pituitary gland increases in size and weight during pregnancy, the change being restricted to the anterior lobe[28]. Zondek showed that the blood of pregnant animals contained large quantities of this hormone of the anterior pituitary, and later, Aschheim and Zondek[29, 30] reported that large amounts were found in the urine of pregnant women. It had also been determined that there were two hormones secreted by the anterior lobe of the pituitary gland which were active in their influence upon the ovary. The first one, called Prolan A or Rho I, causes maturation of the follicles in the ovary, whereas the second, known as Prolan B or Rho II, brings about the luteinization of the follicles and formation of the corpora lutea. Upon these findings, Aschheim and Zondek base their test for pregnancy.

Before describing the Aschheim-Zondek test, we shall first discuss two other tests, also based upon the presence of an increased amount of anterior pituitary hormone in the organism of the pregnant woman. The first of these tests is the SKIN TEST of Pollatschek and Porges. In a letter from Vienna to the *J. A. M. A.* of August 17, 1929, "a simple and reliable skin test for pregnancy" was described; 0.2 c.c. of the hormone of the anterior lobe of the pituitary were injected intracutaneously. "If the woman is not pregnant, a distinct red circle, about one inch in diameter is formed after a few hours at the site of the injection, and remains visible for 24 to 36 hours. In pregnant women, there is no reaction." The authors at first announced an accuracy of approximately 98 per cent., but later modified this statement to an accuracy of only 82 per cent. This work was checked by Strauss[31], who tried the test on 504 patients with very unsatisfactory results. He reported an error of 55 per cent. in the non-pregnant patients, and an error of 70 per cent. in the pregnant patients. Another report[32] also gave similar results. This test, therefore, is apparently without any value.

The BROMINE TEST is the second of these anterior pituitary hormone reactions. The author reported it to be a simple chemical test for pregnancy, testing essentially for the histamine found in the pituitary hormone excreted in the urine. The technic was to mix in a test-tube 2.5 c.c. of urine with 1 c.c. of bromine water, heating the solution to boiling. A positive reaction was indicated by the appearance of a fugitive pink coloration, whereas a negative urine maintained the original yellow color. An accuracy of approximately 95 per cent. was at first reported[33], but this success was soon discredited by a report of 25.7 per cent. error in pregnant cases and 13.1 per cent. error in non-pregnant cases[34]. Personal experience with this test showed an error of about 25 per cent. in both negative and positive cases. Another handicap presented is the great difficulty in the reading of the reaction, since the sought-for color change is so slight and so fleeting.

BROUHA TEST. Brouha and his associates[35] experimented with the effect of the urine of pregnant women upon the genital tract of male mice, finding that in this manner they could secure easily determined macroscopic results, and avoid the use of the microscopic examination so frequently necessary in the original Aschheim-Zondek test. In studying the mice to discover the proper animals susceptible to the test[36], they found that the male mouse reaches puberty between the fifth and sixth weeks. They also found that there does not seem to be any direct relationship between the age and the weight of the mouse, except that mice under ten grams will probably be immature or will just have passed puberty*. They therefore recommend using three to four male mice about five weeks old. Each mouse is injected with from 0.1 to 0.4 c.c. (0.3 c.c. seems to be the optimum dosage) of morning urine daily for from eight to ten days. They are then killed within 24 hours after the last injection†. The whole genital tract shows increased development, but a positive reaction is evidenced by the presence of markedly enlarged, swollen seminal vesicles, distended with a whitish fluid.

The test becomes positive within five to eight days after the first missed period; it becomes negative within four to eight days postpartum. It is regularly positive in ectopic pregnancies and in hydatidiform mole and in chorioepithelioma. In their last paper, Brouha and Hinglais[36] report a total of 400 cases, including a large number of non-pregnant cases with a wide variety of pelvic diseases, with only one false

*Therefore, older mice can be used but the changes are less marked, and errors will undoubtedly creep in. Weight, under 10 gm., should be used as a criterion of immaturity only when a test is urgently needed and no mice of the proper age are at hand.

†Brouha and Hinglais advise as a "rapid method" the killing of the mice on the 6th day, by which time an experienced observer can tell whether the seminal vesicles have enlarged sufficiently to be positive.

positive case, which a repeated test showed to be negative. This is an accuracy of 99.7 per cent. Piéchaud and associates[37] report an accuracy of 100 per cent. in twenty-six cases. White and Severance[38] report the following. "The Brouha reaction was uniformly positive in a group of 60 normal pregnancies, ten ectopic pregnancies, and nine incomplete abortions. However, there were ten false positives in a series of twenty-seven non-gravid cases. Four of these showed hypertrophy of the endometrium, three complained of menstrual irregularity, and one had tuberculous salpingitis."

This test seems to be a reliable reaction, but it has certain objections: In the first place, the large number of injections necessary, 24 to 40, depending upon the number of animals used and the number of days the test is carried out; secondly, the time element, eight to ten days (for this reason alone, this method would not be the test of choice in ectopic pregnancy), and finally, the test may not prove so accurate in the hands of other observers as in those of the original proponents of the test. Further observation will be necessary to determine its exact value.

The last of the tests in the pituitary hormone group is the well-known ASCHHEIM-ZONDEK test, the delicacy of which permits the diagnosis of pregnancy 18 to 21 days after conception has taken place. We shall first consider the technic originally proposed by these authors. They recommended the use of infantile white mice, 18 to 24 days old, and weighing from 6 to 8 grams, thereby assuring the immaturity of the mice and making the injected urine, and not spontaneous maturity, responsible for the resultant reactions. Five mice are required for each test*. As the hormone is most concentrated in the night urine, the first urine passed in the morning is used as the test specimen†. This is filtered and injected in doses of 0.3 c.c. into the mice. Each mouse receives six such injections over a period of 48 hours; for example, Monday at 10 A. M. and 5 P. M., Tuesday at 10 A. M., 1 P. M., and 5 P. M., and Wednesday at 10 A. M. One hundred hours from the time of the first injection, the mice are autopsied and the ovaries examined.

Aschheim and Zondek divided the reactions obtained into three types. The *first reaction* shows maturation of the ovarian follicles and the appearance of estrus. The follicles increase in size and become filled with follicular fluid, causing marked enlargement of the ovary. The ovarian hormone is produced by the ripening follicles (set into action by Prolan A), which, in turn, brings on estrus, manifested by an enlargement of the uterus and the typical changes in the vagina. The *second reaction* is shown by the presence of petechiae in the ovary. These are characteristic hemorrhages into the follicles, appearing macroscopically as either brown or bluish-red spots, each the size of the head of a pin and projecting above the surface of the ovary. The *third reaction* is shown by the presence of corpora lutea in the ovaries. Under the influence of Prolan B, the theca cells, and to some extent the granulosa cells, become luteinized. Only the presence of reactions *two* or *three,* either separately or together, is considered positive for pregnancy; whereas reaction *one* alone merely indicates the presence of Prolan A and the estrus hormone.

A very large literature has grown up concerning this test. A report summarizing the results on almost 5000 published cases[39] indicates an accuracy of approximately 98 per cent., and this accuracy has come to be generally accepted*. Our own experience with this test deals with 143 cases, distributed according to Tables I, II and III. We heartily concur in the many favorable reports already published†.

The original Aschheim-Zondek technic, how-

TABLES SHOWING DATA OBTAINED IN OUR SERIES BY THE ORIGINAL ASCHHEIM-ZONDEK TECHNIC

TABLE I

DISTRIBUTION OF PREGNANT AND NON-PREGNANT CASES ACCORDING TO THE RESULTS OBTAINED

	Pos.	Neg.	% Correct
69 pregnant cases	66	3	95.7
74 non-preg. cases	0	74	100.0
Total	66	77	97.9

TABLE II

DISTRIBUTION OF PREGNANT‡ CASES ACCORDING TO THE DURATION OF THE PREGNANCY

Duration of Pregnancy	Number Cases
4-6 weeks§	31
6-8 "	21
2-3 Months	6
3-4 "	2
4-5 "	3
5-6 "	4
6-7 "	1
7-8 "	1
Total	69

*This number of animals was recommended to permit using one as a control, and also because some might die and because all mice do not react equally to the test. A positive result in one animal is considered positive for pregnancy.

†In order still further to concentrate the hormone, the patient is instructed to restrict fluids the evening before the specimen is collected.

*Mazer and Hoffman[19] disagree with this finding. They report an accuracy of only 73 per cent. in 150 pregnant women, and of 91 per cent. in non-pregnant women.

†We have been using only three mice for each test instead of the recommended five, but we have had no difficulty with the results.

‡Two of these cases were ectopic pregnancies. Two others were fibroids with pregnancy, one of whom would have been operated upon for the fibroid, if the test had been negative.

§Three of these cases which at first gave negative tests, were later proved to be pregnant, two by subsequent positive tests, and one by the lapse of time.

TABLE III

DISTRIBUTION OF NON-PREGNANT* CASES ACCORDING TO SYMPTOMATOLOGY

Types of Cases	Number Cases
Missed 1 period	37
" 2 periods	15
" 3 "	3
" 4 "	3
" 5 "	5
" 6 "	2
Menstruation irregular	4
Metrorrhagia with fibroid	1
After miscarriage	2
Lactation amenorrhea	2
Total	74

*Six of the patients, who missed from 2 to 6 periods each, were of the menopausal type.

ever, has certain distinct disadvantages despite its great delicacy and high degree of accuracy. In the first place, one must constantly breed mice in order always to have on hand a sufficient supply upon which to do the required tests. Moreover, if the mice are not used before the twenty-fourth day, they mature and are of no further value for this test. Furthermore, the time interval of 100 hours, the large number of injections required (a total of 30 for the five mice used), and the small size of the ovaries, which sometimes necessitates the use of microscopic sections for confirmation of macroscopic findings, are all additional disadvantages. As a result, there have been various attempts to modify this technic and obviate these handicaps.

Mathieu and McKenzie[40], because of great difficulty in breeding the mice, began to use one immature rat for each test, injecting 0.5 c.c. subcutaneously twice a day on three consecutive days, the injections being at least four hours apart. The rats are autopsied at the end of 96 hours after the first injection. In 150 cases, they maintained an accuracy of 97.3 per cent. This method, of course, partially eliminates the breeding difficulties and decreases the total number of injections, but does not reduce the time interval required for securing a report.

Eberson[41, 42], also using immature female rats 18 to 21 days old, devised a method for decreasing the time interval to from 36 to 48 hours by concentrating the hormone found in the urine. His technic is as follows: "Two and one-half volumes of 95 per cent. alcohol are added to eight ounces of morning urine and the mixture is placed in the ice-chest at a temperature of from 2 to 4 degrees centigrade for several hours, or over-night, to allow the precipitate to settle out. This step may be hastened by centrifuging the mixture as soon as the precipitate has separated. The precipitate is suspended in 3 to 4 c.c. of physiological saline solution, shaken thoroughly with an equal volume of ether, centrifuged to remove the ether, and the extraction repeated two or three times. The saline solution, after centrifuging and containing the specific hormone freed from the estrus-producing or ovarian hormones, is now ready for injection into rats." This solution is injected into a female immature rat in doses of 1 c.c. twice a day for one or two days, and the animal is autopsied at the end of 36 to 48 hours. This method apparently obviates the breeding difficulties, reduces the number of injections, and shortens the time interval; but, on the other hand, it introduces the technic of concentration, which in itself demands additional time as well as the additional manipulation. In a total of 175 cases, 88 pregnant and 87 non-pregnant, tested by this method, Eberson did not have a single error.

THE FRIEDMAN MODIFICATION OF THE ASCHHEIM-ZONDEK TEST

Still another modification of the Aschheim-Zondek test is that of Friedman. This method, in our own experience, eliminates all the difficulties already enumerated and impresses us as the best pregnancy test developed up to the present time. His method "rests upon three fundamental facts: (1) The ovaries of an isolated, unmated female rabbit contain neither corpora lutea nor corpora hemorrhagica, inasmuch as the rabbit does not ovulate spontaneously, but only after coitus. (2) The urine of pregnant women contains some substance or substances which simulate in their biologic effects the anterior lobe of the pituitary*. (3) The ovary of the rabbit responds to the injection of these substances by the formation of corpora lutea or corpora hemorrhagica"[44].

The rabbits to be used should be, at least, 10 to 12 weeks old, and should have been isolated from males and from other female rabbits† for at least one week, and preferably for two or three weeks. Friedman and Lapham[44] originally recommended that the rabbit be injected intravenously thrice daily for two days with 4 c.c. of morning urine, and then autopsied 48 hours after the first injection. Schneider[45] used a single intravenous injection of 5 to 7 c.c. We have been using a single intravenous injection of 10 to 12 c.c. into the marginal ear vein of the rabbit, not employing any sterile precautions for the injection. Instead of waiting 48 hours before examining the ovaries, we have been operating upon the animals at the end of 24 to 36 hours, in accordance with Schneider's technic. We have had no difficulty with this early

*It is interesting to note that Snyder and Wislocki[43] found that the urine of pregnant macacque monkeys, rats, rabbits, cats, and dogs did *not* produce ovulation when injected into the rabbit. (Some workers have described positive tests on injecting the urine of pregnant monkeys and anthropoid apes into mice.) The authors, therefore, conclude that it is possible that the substance which is producing the reaction with human urine is a species-specific and not an organic-specific.

†The females sometimes "hop" each other and cause a pseudo-pregnancy, which may give false results.

reading in most of our cases. In one case, which was read as negative after 20 hours, a rereading on the following day, after the death of the animal, showed a positive reaction. Therefore, we reoperated on about 15 of our negative animals at the end of 48 hours, and except in one other case, found no change in the results. We have not been sacrificing our animals for each test, but rather have operated on them under anesthesia and closed the wound after examining the ovaries‡. Those that were negative have frequently been used for two or three subsequent tests, thus reducing the expense of the examination. We have also used many of our positive rabbits again, after they have been isolated for about two weeks§. In these animals, one can readily distinguish between the old corpora hemorrhagica and corpora lutea, which, by that time, have shrunk to a much smaller size than the fresh corpora hemorrhagica and corpora lutea. Since the ovaries of the rabbit are much larger than those of the mice and rats, the reactions are correspondingly more prominent and very simple to read, especially after one has seen a few positive and negative ovaries.

On later re-injecting the positive rabbits, we have had a few animals that apparently died of anaphylactic shock, as determined by autopsy. When the urine so used was subsequently injected into fresh animals, the latter survived. Friedman and Lapham reported 3 of 112 specimens of sufficient toxicity to kill the rabbits. In our series of 136 cases, we have had 9 toxic specimens*. Six of the injected animals began to have convulsions immediately after the injection, and died within two to three minutes. Three other animals that also had convulsions after injection of the urine, recovered after artificial respiration, which was begun at once and continued for about 10 to 15 minutes. It is rather interesting to note that those specimens which were toxic to the rabbits did not kill the mice into which they were also injected, and, on the other hand, those specimens which were fatal to the mice, had no harmful effect on the rabbits.

We have found that the Friedman modification is quite as delicate as the original Aschheim-Zondek test. According to Schneider, "The data obtained in these cases indicate that the reaction appears at approximately 18 to 21 days following the intercourse responsible for the pregnancy. If these observations are proved to be correct by subsequent investigation, they will serve as additional evidence to substantiate the theory[46, 47] that the hormone causing the reaction may be dependent on the development of the decidual tissue instead of entirely on anterior pituitary product as was at first maintained[27]. Further evidence supporting this contention is derived from the fact that the only conditions other than pregnancy causing the reaction are hydatidiform mole and chorioepithelioma[48]." The test becomes negative rapidly postpartum, most cases being negative within 48 hours after delivery. Thus, this test serves as a good method for determining the death of the *entire ovum* but not of the fetus alone*. We have had four cases where the fetus had died, but the placental circulation continued. In all of these, positive results were obtained. We have also had two cases wherein the entire ovum was passed, a short time after a negative result had been reported. (See cases 43, 84, and 85 in the illustrative case histories.)

The literature up to date (July, 1931) on the subject of the Friedman modification of the Aschheim-Zondek test is summarized in Table IV.

TABLE IV

SUMMARY OF THE REPORTS OF THE RESULTS OBTAINED BY THE FRIEDMAN MODIFICATION OF ASCHHEIM-ZONDEK TEST

Authors	Pos.	Neg.	% Correct
Friedman and Lapham[44]	47	51	100*
Schneider[45, 48]	86	114	96†
Reinhart and Scott[49]	68	82	98.7‡
Magath and Randall[50]	38	47	97.6§
Total	239	294	98.1

*No errors in any of these cases.

†25 of the positive cases were known pregnant controls and 25 were known non-pregnant. Of the 150 test cases, 2 negatives yielded false positives, but both later gave negative results. In one instance, the error was due to some confusion in the markings of the rabbit, and in the other to improper interpretation of the macroscopic findings. Six urines that were secured at too early a period after conception gave false negatives. All gave positive reactions on repetition of the test at a later date.

‡Two urines which first gave false negatives, later gave positive results. In one case, the urine was sent from a different hospital and may not have been the correct specimen. In the other, examination of the rabbit at the end of only 24 hours showed apparently negative ovaries.

§In one case, where the rabbit used had recently been in the same cage with a male, a false positive was secured. In another, where the urine was probably secured at too early a period after conception, a false negative was reported. This latter case gave a correct positive on repetition of the test at a later date.

Our own series consists of tests performed upon 136 patients†. Seven of these cases were positive controls, a definite diagnosis of pregnancy having been previously established clinically. The remaining cases were undetermined,

‡We have had four pregnant cases in which one ovary was negative and the other positive. Therefore, both ovaries should always be examined where the first one seen is negative.

§In our experience, rabbits that are positive on two occasions, should not be used again, because the ovaries become so scarred that there may not be room for new follicles to develop, and false negatives may result.

*Some of the patients whose urine proved to be toxic were later found to have been taking various abortifacients to induce menstruation. This possibility should be determined when instructions for collecting the specimen are given.

*Eberson and Silverberg[43] have suggested a new method for diagnosing death of the *fetus alone*. In microscopic sections of the ovaries of rats which have been injected with urine from patients with dead feti, they found "heretofore unrecognized tinctorial and structural changes in the follicular cells seen in histological sections. . . . The microscopic picture in the corpora lutea is characteristic of retrograde changes and is different from the typical luteinization in these cells."

†Sixty-five of these cases have been reported in a previous communication to the *New England Journal of Medicine*. 205: 566, 1931. Since this present article was submitted for publication, we have had 120 additional cases with an accuracy of 100 per cent. in the positive cases, and only one false positive in the negative cases.

except for six specimens which were submitted for a question of death of the entire ovum. All these specimens were submitted by various physicians for the establishment of a diagnosis of the presence or absence of pregnancy. All but three of these cases have been followed, and in all of them the correctness of the diagnosis has been established, except as indicated below. The results are summarized in Tables V, VI, and VII.

TABLES SHOWING DATA OBTAINED IN OUR SERIES BY THE FRIEDMAN MODIFICATION

TABLE V

DISTRIBUTION OF PREGNANT AND NON-PREGNANT CASES ACCORDING TO THE RESULTS OBTAINED

	Pos.	Neg.	% Correct
62 pregnant cases	60	2	96.8
68 non-preg. cases	3	65	95.4
Total (130)	63	67	96.1

TABLE VI

DISTRIBUTION OF PREGNANT CASES ACCORDING TO THE DURATION OF THE PREGNANCY

Duration of Pregnancy	Number Cases
4-6 weeks*	27
6-8 "	20
2-3 months	4
3-4 "	2
4-5 "	1
5-6 "	5
6-7 "	2
7-8 "	1
Total	62

*Two of these cases, which at first gave negative results, were later proved to be pregnant. They later gave positive results on repetition of the test.

Two of these cases were ectopic pregnancies, the positive findings being later confirmed by operation. Two others were fibroids with pregnancy, one of whom would have been operated upon for the fibroid, if the test had been negative.

TABLE VII

DISTRIBUTION OF NON-PREGNANT CASES ACCORDING TO SYMPTOMATOLOGY

Types of Cases	Number Cases
Missed 1 period†	33
" 2 periods	17
" 3 "	2
" 4 "	3
" 5 "	2
" 6 "	2
" 7 "	1
Menstruation irregular	2
Metrorrhagia with fibroid	1
Ovarian cyst	1
After miscarriage	2
Lactation amenorrhea	2
Total	68

†Three of these cases, which at first gave positive results, were later proved to be non-pregnant. Two were performed on uncontrolled rabbits, the rabbits being injected on the same morning that they were brought into the laboratory.

In order to compare the relative accuracy of the original Aschheim-Zondek technic and the new rabbit modification, we checked 127 of the above cases by injecting into mice the urine used. Of these, 40 were still further checked by the Ninhydrin Flocculation test. The results are summarized in Table VIII.

TABLE VIII

DISTRIBUTION OF PREGNANT AND NON-PREGNANT CASES ACCORDING TO THE ACCURACY OBTAINED BY THE THREE TESTS

	Rabbit		Mice		Nin. Floc.	
	No.	%	No.	%	No.	%
Correct Positives	59	96.8	59	100	17	77.4
False Positives	2	3.2	0		5	22.6
Correct Negatives	63	95.5	65	95.6	15	83.3
False Negatives	3	4.5	3	4.4	3	16.7
Total*	127		127		40	

*57 of the positive cases and 63 of the negative cases checked by both the mouse and rabbit tests, that is, a total of 120 cases.

The two cases that have false positives by the uncontrolled rabbits gave correct negatives by the mouse test, and another two cases that gave correct positives by the rabbit test, gave false negatives by the mouse tests.

The two cases that at first gave false negatives by the rabbit test, gave correct positives by the mouse test.

In one case, both the rabbit and mouse tests gave a false negative.

In the 40 cases correlated by the Ninhydrin Flocculation test, there was agreement in 32 cases, that is, in 17 of the positive cases and 15 of the negative cases. Five of the cases gave false positives, and three gave false negatives.

In the following case histories are illustrated some of the problems in diagnosis which were materially assisted by the use of these pregnancy tests:

Normal Non-pregnant.

CASE 13. Nullipara; aged 22; periods had always been regular. Last period was on Jan. 22, 1931. Had intercourse on Feb. 12, 1931. No period occurred in February. Mouse and rabbit test on March 3, 1931 were negative. Patient had a normal period on March 18, 1931.

CASE 25. Nullipara; aged 18; periods had always been regular. Patient admitted promiscuous intercourse for the last two years. Last period was on January 24. She has had no symptoms of pregnancy, but the uterus was somewhat enlarged and soft on vaginal examination. She also complained of some pain and tenderness in the left lower quadrant. Mouse and rabbit tests on March 16 were negative. Patient had a normal period on March 22.

CASE 27. Nullipara; aged 29; married 2 years but had never been pregnant. Periods began at 16, were always regular, lasted 2-3 days, flow rather scanty, no dysmenorrhea. Last period on January 21. Has had no symptoms of pregnancy other than some urinary frequency and fullness and tenderness of the breasts. Patient was rather obese, and vaginal examination was unsatisfactory. Mouse and rabbit tests on March 21 were negative. Patient had a normal period on April 1.

CASE 118. Nullipara; aged 26; married eight months but had never been pregnant. Periods had always been regular. She had an appendectomy

and uterine suspension performed in January, 1931. The operation was followed by a severe, bilateral phlegmasia alba dolens, which lasted for six weeks. The patient has been in poor general health since then, having lost almost 20 pounds weight since the operation. Last period was on April 14. Rabbit test on June 11 was negative. Patient menstruated on June 14.

CASE 130. Nullipara; aged 20; periods were always regular until the last year, during which she has been flowing twice a month. During this last year, she has been having intercourse at frequent intervals, and became infected with gonorrhea. Her last period was on April 30. She entered the hospital on June 20, complaining of severe pain in the right lower quadrant; a tentative diagnosis of chronic salpingitis with question of ectopic pregnancy was made. Mouse and rabbit test on June 22 were negative. Operation on June 27 showed chronic salpingitis without any pregnancy.

Menopause.

CASE 34. Quadripara; aged 41; last period on January 3. Her periods have never been irregular. She has had no symptoms of pregnancy other than some nausea. Her uterus seems somewhat enlarged on vaginal examination. The patient feels that she is pregnant and is very nervous and excited. Mouse and rabbit tests on March 27 were negative. The patient felt somewhat reassured. She later reported a normal menstrual period on April 17.

CASE 38. Tertipara; aged 50; youngest child 20 years old. Her periods have been somewhat irregular during the last year, and she has had occasional headaches and some nausea. Last period on December 10, 1930. Had intercourse on February 23, 1931. Rabbit test on April 7 was negative. Patient reported that she menstruated on April 23.

Ectopic Pregnancy.

CASE 26. The patient, aged 19, has one child six months old. Her last period was on January 18. She has had no nausea or vomiting, no urinary frequency, no breast symptoms. Vaginal examination shows her uterus to be slightly enlarged and soft, and slight tenderness in the left vault was also elicited. Mouse and rabbit tests on March 16 were positive; the ninhydrin flocculation test was negative. On March 20, the patient began to have severe pain in the left lower quadrant, and was sent into the hospital by her physician. There she was operated upon for an ectopic pregnancy, the diagnosis being confirmed by the operative findings.

Lactation Amenorrhea.

CASE 2. The patient, aged 27, has one child two months old, which she is nursing. She began to have some nausea on January 31. No other symptoms of pregnancy elicited. A rabbit test on February 3 was positive. The patient had an incomplete miscarriage on February 15, the diagnosis being confirmed by the findings on curettage of the uterus.

CASE 87. The patient, aged 29, has one child aged 4 months, which she is nursing. Stained for one day in March. She is now afraid that she is pregnant again, although she has no symptoms of pregnancy. Rabbit test on May 14 was negative. The patient menstruated on May 18.

Normal Pregnancy.

CASE 136. Primipara; aged 28; periods always regular; last period on June 1. Intercourse took place on June 17. Patient did not menstruate on June 29 as expected. She had no other symptoms of pregnancy. Rabbit test on July 3 was positive. Repetition of mouse and rabbit tests on July 9 were again positive. Physical examination shows some changes in the size and consistency of the uterus.

CASE 140. Primipara; aged 19; periods have always been regular. Her last period was on June 3. Intercourse took place on June 18. Rabbit test on July 6 was positive. Repetition of test on July 10 was also positive. Patient is beginning to have some nausea and vomiting. Physical examination also shows some changes in the size and consistency of the uterus.

Postponement of Operation.

CASE 64. Quadripara, aged 32; periods generally regular, but have been somewhat irregular for the last year. Has had two miscarriages during the last three years. Last period was on February 28. Patient has had no symptoms of pregnancy. Vaginal examination showed the uterus to be slightly enlarged but not soft; the cervix was firm, scarred, and badly lacerated. A rabbit test was performed to rule out pregnancy in order to permit of repair of the cervix and of a moderate degree of cystocele which was present. The rabbit test of April 22 was positive, and the operation was postponed. The patient miscarried on July 2.

Dead Fetus

CASE 43. Primipara; aged 31; last period on January 17. On April 7, the patient began to flow and stained two napkins. She was put to bed and given morphine and sodium amytal. The flowing stopped shortly thereafter, and there was no flow until April 9. At 4 P. M. on that day she suddenly began to have cramps in the lower abdomen, which continued to increase in severity. She began to flow again at 5 P. M. and at 7 P. M., she passed practically the complete ovum. Examination of the uterus with the finger, under gas-oxygen anesthesia, showed the cavity to be completely empty. Mouse and rabbit tests of the first urine voided on the morning of April 9 were both negative. This would seem to indicate that the ovum had apparently died several days before, and that the miscarriage was a result of this death.

CASE 84. Quintipara; aged 36; last period on September 15, 1930. She has a chronic nephritis with toxemia of pregnancy, a blood pressure of 180/110, and blood chemistry findings corresponding to her condition. The fetus had apparently died in April, since which time she had felt no motion. No fetal heart could be heard. Rabbit test on May 14 was positive; a mouse test on May 12 was negative. After induction of labor, a dead fetus was delivered on May 14. The placenta was extensively fibrosed.

CASE 85. Quadripara; aged 33; last period on September 28, 1930. She had a preëclamptic toxemia condition. The fetus had probably died early in May, since which time she had felt no motion. There had been no enlargement of the uterus over a period of two weeks, and the fetal heart could not be heard on repeated examination. Mouse and rabbit tests on May 12 were both positive. Patient went into labor spontaneously, and delivered herself of a dead fetus

on May 14. The placenta was in fairly good condition.

Hypopituitary Cases.

CASE 7. The patient, aged 30, had had one miscarriage in December, 1929, and another one in July, 1930, at three months, the latter being followed by dilatation and curettage. (Intensive study of this patient had led to a diagnosis of a hypopituitary condition.) Her last period was on December 24, 1930. Patient had no symptoms of pregnancy, and was informed, after examination, that she was probably not pregnant. A mouse test on February 16, 1931, was positive. On April 1, 1931, the patient miscarried.

CASE 90. The patient, aged 31, had had two previous miscarriages and an operation for ectopic pregnancy. Her last period was on April 7, and pregnancy probably began about the 15th of April. Patient began to have symptoms of nausea and vomiting very shortly thereafter. Mouse and rabbit tests on April 14 were negative. Patient was informed of the results of the test, but refused to believe them. A repetition of both tests on May 21 gave the same results. This second finding led to the patient's having an intensive study done, with the result that a diagnosis of a hypopituitary condition was made. Repetition of the tests on June 4 gave positive results. Repetition on June 18 gave a positive reaction by the mouse test, and a negative result by the rabbit test. (There was some question as to whether this particular rabbit was of the proper age for the test, but as no other one happened to be on hand, it was used.) This case would seem to illustrate the possibility that a hyposecretion of the pituitary gland, in those rather uncommon cases where it occurs, may interfere with obtaining a correct result by those pregnancy tests which depend upon the pituitary hormone for their accuracy.

CONCLUSIONS

1) Of all the pregnancy tests thus far developed, the Aschheim-Zondek reaction seems to be the most reliable, having given the highest percentage of accuracy in the hands of most workers.

2) Of the various technics for performing the Aschheim-Zondek test, Friedman's modification, using the rabbit, seems to us to be the best, from the point of view of delicacy, accuracy, simplicity, rapidity, and ease of reading the results.

3) The best technic seems to be the single intravenous injection of 10 to 12 cc. of the first urine voided in the morning and the operating on the rabbit at the end of 30 hours.

4) If the test is negative, the rabbit may be used again immediately or at some later period; if positive, the rabbit can be used again after a period of isolation for 10 to 14 days, but should not be used a third time, if positive by the second test.

5) This test can be used for the differential diagnosis of pelvic masses or neoplasms, in menstrual irregularity or amenorrhea of various origins, and for ruling out pregnancy where some form of instrumentation of the uterus is to be undertaken.

6) In the uncommon cases of pregnancy in hypopituitary patients the tests may not become positive until the pregnancy has advanced to the third or fourth month. These patients frequently miscarry. Much more study on them is needed before the exact interpretation of their status in relation to these tests can be determined.

7) Death of the entire ovum may be diagnosed, and the presence of active placental tissue in incomplete abortions, hydatidiform mole, and chorionepithelioma may be determined. With further study (see footnote p. 179. Eberson and Silverberg[42], etc.), it may be possible to diagnose death of the fetus alone.

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CINCHOPHEN POISONING*

A Report of Three Cases

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SINCE the introduction of cinchophen into therapeutics in 1908, approximately 80 cases of poisoning following its administration have been reported. The recorded toxic manifestations usually have taken one or more of the following forms: (1) cutaneous manifestations, such as pruritis, angioneurotic edema, urticaria, macular and papular rashes, first reported by Phillips[1] in 1913; (2) anaphylactoid reactions characterized by neurocirculatory disturbances associated with rapid pulse and lowered blood pressure, as described by Scully[2] in 1924; (3) gastro-intestinal disturbances including simple ulcers of the mouth, pyrosis, nausea, vomiting and diarrhea, reported by Schroeder[3] in 1922; and (4) liver involvement as indicated by the appearance of jaundice, first noted by Worster-Drought[4] in 1923.

The hepatic damage produced by cinchophen may range from a transitory toxic hepatitis, with subsequent complete recovery, to an acute yellow atrophy, terminating fatally. Cabot[5], in 1925, was the first to demonstrate a fatal case of liver atrophy due to Weldona tablets. Rabinowitz[6], in 1930, reported nine cases of his own and reviewed forty-one cases from the literature. In these fifty cases there were twenty-five deaths, with twenty autopsies confirming the diagnosis of toxic hepatitis and liver atrophy as the cause of death. Similar cases have since been reported by Parsons and Harding[7], Beaver and Robertson[8], Ross[9], Cabot[10], and Sherwood and Sherwood[11].

Three cases of cinchophen poisoning have been seen recently at the Beth Israel Hospital. One of the cases (Case I) presented the idiosyncratic type of reaction to cinchophen, while the other two cases suffered from acute toxic hepatitis.

CASE REPORTS

CASE I. H. S., a single white waiter, 38 years of age, entered the hospital on November 23, 1930, complaining of vomiting of one week's duration. During the previous year he had been practically bedridden because of recurrent attacks of arthritis involving his ankles and wrists. For this condition he had received, at irregular intervals, 0.3 gms. of cinchophen daily. The exact total amount of cinchophen taken could not be determined. The present attack of vomiting began apparently after taking only one tablet of cinchophen.

Physical examination revealed a poorly nourished man with infectious arthritic changes and muscular atrophy in both elbows, hands, and ankles. There was slight dullness and bronchial breathing over the left upper lung, and a few crepitant râles in the left axilla. The rectal temperature was 102.5° on admission, the pulse rate 130, and the blood pressure 150 mm. of mercury, systolic, and 60 mm. of mercury, diastolic.

Laboratory Data: The *urine* during the first three days in the hospital showed 5-10 red blood cells, 5-10 white blood cells, and many granular and hyaline casts. The specific gravity varied from 1.002 to 1.022. Examination of the blood showed no anemia or leucocytosis and a normal differential count. The blood non-protein nitrogen, creatinine, and serology were all normal. Two *stool examinations* were negative. Prostatic smears were negative. The phenolsulphonephthalein renal function test was 25 per cent. in 2 hours 10 minutes.

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Roentgenograms of the pelvis, elbows, ribs, hands, and feet showed no evidence of bone destruction.

Clinical Course: The vomiting ceased during the first day of his stay, and the temperature fell to normal. He was given a soft solid diet, with large amounts of fluids. On the fifth day he was able to be up and about the ward. The red blood cells and the casts had disappeared from the urine by the sixth day. Because of some uncertainty regarding the cause of his symptoms, he was given, on the tenth day, 0.3 gms. of cinchophen at 5 P. M. At 8 o'clock he became flushed, very excited, and salivated profusely. At 9 o'clock his rectal temperature was 102.6°; his pulse rate increased from 80 to 100, and his blood pressure, in millimeters of mercury, fell from 100, systolic and 60, diastolic to 80, systolic and 50, diastolic. He began to vomit. The vomiting continued through the night. The following day he showed a macular rash over the trunk. The urine remained normal. He did not feel well until 48 hours after cinchophen was administered. He was discharged improved on December 5, 1930.

Comment: This case illustrates both the anaphylactoid type of reaction noted by Scully[2] and the gastro-intestinal disturbances described by Schroeder[3]. Thus he showed vomiting, fever, rise in pulse rate, drop in blood pressure, and a macular rash following the administration of a single dose of 0.3 gms. of cinchophen. The entire reaction in this case was apparently idiosyncratic in nature.

CASE II. E. B., a married white woman, 47 years of age, came to the medical out-patient department of the Beth Israel Hospital on January 12, 1931, complaining of arthritic pains in both hands, fingers, and feet of three years' duration. A diagnosis of chronic infectious arthritis was made, and oxyl-iodide,* two capsules daily, was prescribed on February 16, 1931. This she took for two weeks, when she developed itching of the palms, feet and scalp, and she stopped taking the medicine. The itching disappeared within a week, after taking cathartics and saleratus baths. She then noticed loss of appetite, a sense of fullness in the epigastrium, and some nausea and heartburn. On March 17, she noticed that her skin was getting yellow. This became very severe in two days, and was accompanied by general malaise. On March 26, she was admitted to the medical ward for treatment.

Physical examination revealed a moderately obese and markedly jaundiced white woman. The upper border of the liver was in the fourth interspace, and the lower border was palpated four fingerbreadths below the right costal margin. Otherwise the physical examination was negative.

Laboratory Data: The *urine* showed a slight trace of albumin, and a large amount of bile. The *blood* showed no anemia or leucocytosis and a normal differential count. The icteric index was 132. The non-protein nitrogen was 30 mgs. and the blood urea nitrogen 12 mgs. per 100 c.c. of blood. The direct van den Bergh four days after admission was 26.1. The plasma fibrinogen ranged between 0.343 and 0.493. The serum calcium was 12.5 and the blood sugar content 81 mgs. per 100 c.c. *Gastric analysis* showed normal figures for free and total acid. Four *stool examinations* showed nothing abnormal. Bile was present in every specimen. *Roentgenograms* of the gall bladder showed no evidence of calculi of the opaque variety.

Clinical Course: The patient's temperature, pulse and respiration remained normal. The systolic blood pressure averaged 120 and the diastolic, 70 millimeters of mercury. The patient was treated by rest in bed, a high carbohydrate, low fat diet, with five units of insulin before each meal, and 25 gms. of magnesium sulphate every morning. She remained symptom-free throughout her entire stay in the hospital. The liver decreased in size gradually, and at the time of discharge was not palpable. The jaundice lessened progressively, and at the time of discharge there was only a slight icteric tinge present. The albumin disappeared from the urine within five days, and the bile within twenty days. The icteric index was 25 at the time of discharge (May 1, 1931), and the van den Bergh was 0.74, giving a diphasic reaction. The bromphenolsulphonephthalein liver test done a month after admission showed 50 per cent. retention at the end of five minutes, and 10 per cent. retention at the end of 30 minutes. When next seen on May 15, 1931, she was symptom-free, and showed an icteric index of 12. On June 30, the icteric index was 6, and the bilirubin liver function test was normal.

Comment: This middle-aged woman, who had never had any hepatic disease, developed an acute toxic hepatitis after taking only 5.6 gms of cinchophen over a period of two weeks. The history and clinical course leave no doubt that cinchophen was the toxic agent.

CASE III. C. L., a married white woman, 47 years of age, came to the medical out-patient department of the Beth Israel Hospital on April 14, 1931, complaining of progressive, painless jaundice of five weeks' duration. She had enjoyed perfect health until eight weeks before admission to the hospital, when she began to have dull aching pains in the calf and thigh muscles of her left leg. Her family physician gave her atophan tablets of which she took 36 to 48 tablets within one week, and without relief. She was then given oxyl-iodide capsules, and took 24 capsules in a week. About five weeks before admission to the hospital, she developed an extreme itching all over her body, and burning micturition. At the same time her children noticed that she was getting yellow. There was anorexia, nausea, and a sense of fullness in the epigastrium. The jaundice gradually increased in intensity, in spite of cathartics and medication given her by the family physician who finally advised her to enter the hospital.

Physical examination revealed a markedly jaundiced woman, with excoriations of the skin from scratching. The upper border of the liver was in the fourth interspace, and the lower border was palpated four fingerbreadths below the right costal margin. The rest of the physical examination was entirely negative.

Laboratory Data: The *urine* showed a maximum specific gravity of 1.020 and four plus bile. There was no albumin. The *blood* showed no anemia or leucocytosis and a normal differential count. The blood sugar content was 78, the non-protein nitrogen 26, and the blood urea nitrogen 11.3 mgs. per 100 c.c. The *plasma fibrinogen* ranged between 0.428 and 0.336 per cent. The *icteric index* was 120 on admission. *Gastric analysis* showed normal figures for free and total acid. The *stools* showed bile on repeated examinations. *X-rays* of the gall bladder and the gastro-intestinal tract were entirely negative.

Clinical Course: The patient's temperature, pulse, and respiration remained essentially normal. She was treated by rest in bed, a high carbohydrate, low fat diet, with five units of insulin before each meal, and 25 gms. of magnesium sulphate every morning. The nausea, pruritis and jaundice gradually diminished. The liver gradually decreased in size, and at the time of discharge, on June 8, could not be palpated. The bile in the urine disappeared within 16 days. The icteric index fell gradually and was 25 at the time of discharge The bromphenolsulphonephthalein liver function test done during the fifth

*Each capsule of oxyl-iodide contains 0.2 gms. of phenyl-cinchoninic acid.

week of her stay in the hospital showed 130 per cent. retention at the end of five minutes, and 70 per cent. at the end of 30 minutes. When repeated a week later, it showed 120 per cent. retention after five minutes, and 55 per cent. after 30 minutes. When seen in the out-patient department on June 25, 1931, she was entirely symptom-free. On July 7, 1931, the icteric index was 8, and the bilirubin liver function test was normal.

Comment: This is a case of acute toxic hepatitis in a middle-aged woman who had never suffered from any hepatic disease. The history leaves no doubt that the toxic agent was cinchophen. She had taken about 28.8 grams of cinchophen during the two weeks preceding the onset of toxic symptoms.

DISCUSSION

A study of the cases of cinchophen poisoning reported in the literature reveals that the toxic manifestations have no relation to the amount of cinchophen taken and that such manifestations are often deferred for weeks after the drug has been discontinued. Thus, a patient of De Rezende's[12] developed toxic hepatitis after taking only 3.0 gms. of cinchophen, while Hench and Rowntree[13] saw a patient who had taken large amounts of cinchophen over a period of eighteen years without the slightest discomfort or disability. This would seem to indicate that certain predisposing conditions must obtain which sensitize the liver to the toxic action of cinchophen preparations. Such predisposing conditions, according to Rabinowitz[5] are: gall bladder disease, cirrhosis of the liver, pregnancy, chronic alcoholism, chronic nephritis, a past history of jaundice, and the sensitization of the liver to protein whether by surgical trauma, inhalation, ingestion, or parenteral injections. These contraindications to the use of cinchophen, and the inability of Willcox[14] and Loewenthal and his associates[15] to avoid severe toxic reactions by exercising every known precaution in their cases, make one doubt whether cinchophen-containing preparations can be administered with any degree of safety.

Cinchophen achieved great popularity chiefly because of its striking effect on the elimination of uric acid, and its alleged tophi-removing powers ("Atophan"). Its effect on tophi has proved disappointing, but it has been found to be an effective analgesic, much like the salicylates. Hence, its inclusion in many "pain killers", "rheumatism cures", and other secret nostrums. Since there are many other analgesics quite as effective as cinchophen and without its insidious dangers, it would seem wise to avoid using any preparations suspected of containing cinchophen whenever possible.

CONCLUSION

1. Three cases of cinchophen poisoning are reported. One patient showed an anaphylactoid type of reaction, while the other two cases suffered from an acute toxic hepatitis.

2. One of the patients developed an acute toxic hepatitis after taking only 5.6 grams of cinchophen, while the other case took 28.8 grams.

3. The dangers of cinchophen administration are stressed.

4. Since there are many analgesics as effective as cinchophen, and without its insidious dangers, it is thought best to avoid using it whenever possible.

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A PRACTICAL ENDORSEMENT OF PRESIDENT HOOVER'S PLEA

Believed to be the first industrial organization to take definite steps toward following up President Hoover's plea for a more active national interest in the cause of children's rights, the Kellogg Company of Battle Creek, Michigan, recently conducted a six-day, free health clinic for all Kellogg employees' children under six years of age.

Nearly three hundred children received thorough health examinations from medical specialists in Battle Creek, during the six-day period. The examinations were sponsored by the Kellogg Coöperative Aid Society, a welfare organization of which each employee is a member. Eight local physicians conducted the examinations, in coöperation with the Kellogg Company Hospital Staff. The work included x-rays, examination of teeth, ear, nose and throat; skin test for tuberculosis, and a thorough body examination of the heart, lungs, posture and other general health aspects.

A summary of the findings was made available to each of the parents, together with suggestions which will make for better health, happiness, and productivity in the life of each child.

The examinations were in no way compulsory.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICAL-PATHOLOGIC EXERCISES

EDITED BY RICHARD C. CABOT, M.D.
F. M. PAINTER, A.B., ASSISTANT EDITOR

CASE 18041

A WEEK'S HEADACHE AND VOMITING

NEUROLOGICAL DEPARTMENT

A Canadian girl twenty-one years old, a stitcher in a factory, entered in coma of two days' duration. The history was given by a very intelligent person, the daughter of the woman who had taken care of the patient since she was seven months old.

Nine weeks before admission she had an attack of vomiting. Three weeks later she complained of trouble with her eyes; said that things looked like "waves". There was no definite diplopia. Thirteen days before admission she had nausea, vomiting and pain in her stomach and head. She felt very ill but continued to work for three or four days. Eight days before admission she felt unable to work. A physician found a stiff neck. She did not retain anything by mouth. The vomiting was usually with some warning and never definitely projectile. Five days before admission she seemed a little brighter and vomited less. The pain in her head and at the back of her neck continued. Two days before admission she became hard to rouse and started to vomit again. She lay so as to avoid the light. On the morning of admission a consultant found the neck very stiff.

A cough ("bronchial") went back for several years. She had had gradual loss of about 20 pounds in the past six years.

Her mother lost her mind soon after the birth of the patient and died five years later of consumption.

The patient had had measles. She had had sore throats until two years before admission, when she had tonsillectomy and adenoidectomy. For several years she had had trouble with her eyes and head, probably headaches and some eye strain. For several years she had had cough with a small amount of sputum, slightly streaked. She had always been nervous and worried easily.

Clinical examination showed a fairly well nourished young girl difficult to rouse, lying quietly in bed with her head held back. Her pharynx and soft palate were covered with grayish white patches. The spine and neck were held rigid, preventing flexion. Her lungs showed some increase in resonance posteriorly over the bases. The abdomen was distended and very tympanitic. The full bladder was felt up to the umbilicus. The cranial and neural reflexes, knee jerks and ankle jerks were increased, the triceps, biceps, radials and plantars normal, the abdominal reflexes absent. The first cranial nerve was not tested; the others were normal. Kernig was positive. The fundi appeared slightly myopic. The veins showed a little tortuosity. Otherwise the fundi were normal at two examinations.

The amount of urine was 37 to 45 ounces, the specific gravity 1.014. There was a very slight trace of albumin, a slight trace of sugar, 2 to 4 leukocytes and rare red cells at the single examination. Blood examination showed 6,500 to 7,000 leukocytes, 80 per cent hemoglobin, 74 per cent polynuclears. Lumbar puncture on the day of admission in the third-fourth lumbar space showed an initial pressure of 450, dynamics normal. 12 cubic centimeters of clear colorless fluid was removed. There was no clot. The fluid showed 57 lymphocytes, total protein 116, sugar 22.8, alcohol positive, ammonium sulphate strongly positive, Wassermann negative, chlorides 591, colloidal gold 0000133211. Another puncture the following day showed an initial pressure of 250, pulse and respiratory excursions normal. 25 cubic centimeters of clear colorless fluid was withdrawn. A pellicle formed. There were 163 cells, 85 per cent lymphocytes, 15 per cent polynuclears, total protein 118, sugar 19.5, alcohol and ammonium sulphate strongly positive, chlorides 585, colloidal gold 0000123221.

X-ray examination showed very fine soft mottling throughout both lung fields. There were no calcified masses and no areas of consolidation. The diaphragm was in the usual position, sharply outlined.

The patient showed no change in condition for the first six days except a slight improvement in taking nourishment. The afternoon of the seventh day the pulse rose. The following morning she showed a decided change for the worse, with rise in pulse and respirations. Chest examination showed generalized transmitted tracheal and medium coarse bronchial râles at both bases. Then without any marked change except a slight rise in respiration the patient quietly stopped breathing.

CLINICAL DISCUSSION

BY RICHARD C. CABOT, M.D., AND GEORGE W. HOLMES, M.D.

NOTES ON THE HISTORY

DR. CABOT: Most of the causes of coma do not occur at twenty-one. The first two we think of are diabetes and tuberculous meningitis. We

think less definitely of the comatose stages of infectious diseases, which of course would probably be mentioned in the entrance note. The comatose stage of pneumonia for example is not at all probable with this history. Sunstroke of course anybody can have and also alcoholism and morphine poisoning. These can be excluded by the history. Diabetes and tuberculous meningitis I mention as the two most likely to come here without any history explaining them.

I think it is very striking how people go on working as this girl did with what looks like meningitis. I have seen it in a number of cases.

The history of the present illness is typical of tuberculous meningitis. There is a possibility of poliomyelitis, a bare possibility of encephalitis, but not much more. The cough that went back for several years suggests that it quite possibly came from a tuberculous lung trouble. The gradual loss of weight fits this idea. The fact that her mother died of consumption also fits it, because the patient was presumably exposed. We have no statement of that fact, which we need, but it is fair to assume it.

"Headaches and eye strain of long duration." That is the sort of thing that probably confused her physicians and relatives. Eye symptoms and headache,—she had had it all before for years. They said, I suppose, "This is just more of her old trouble."

NOTES ON THE PHYSICAL EXAMINATION

In the clinical examination we are looking for evidence of meningitis and very possibly of pulmonary tuberculosis.

Those grayish-white patches on the pharynx and soft palate must be investigated with the possibility of diphtheria. They are however probably local low grade infections occurring in connection with the coma but of no importance.

Increased resonance at the bases is not of much importance. We are looking for râles at the apices. We shall have to assume that the lungs are normal.

A full bladder is common in a comatose condition.

The stiff neck and positive Kernig are strong evidence for meningitis.

The fact that the fundi were normal is important of course in ruling out tumor and kidney trouble, two of the possible causes of coma at her age.

There is nothing remarkable in the urine examination that I see.

The lumbar puncture is what we are waiting for. It showed quite a high initial pressure. The fluid was colorless, as we should expect it to be. There was no clot, as we should expect. A pellicle formed in the second lumbar fluid. It is much more likely to form the second time than the first time. The lumbar fluid gives us evidence of tuberculous meningitis, tuberculous not because we have any tubercle bacilli there, but because there is nothing else in the case to explain such a fluid. At her age and in the absence of any evidence of syphilis or poliomyelitis or sleeping sickness, we cannot get this picture from anything else. I think it is fair to say that none of those diseases are suggested by anything in the record.

That mottling throughout the lung fields is interesting to see. This x-ray examination was of course done in the wards with a portable machine.

DR. HOLMES: The mottling is very fine and rather indefinite. We could possibly get such a picture on a film taken during expiration instead of inspiration. I think that is rather more than we get in any normal lung. We ought to interpret it as a type of miliary process. Of course in a young person it is most likely to be miliary tuberculosis.

DR. CABOT: Could it be due to passive congestion from heart trouble?

DR. HOLMES: No; I think the heart would be larger, with prominent hilus shadows and more definite trunks. The heart looks a little large here. It is I think magnified because of the way in which the films were taken. I should say miliary tuberculosis or nothing. The appearance might be due merely to the fact that the lungs are not well filled with air.

DR. CABOT: If it were an elderly person wouldn't you have to think of malignant disease?

DR. HOLMES: It is possible to get a picture like this from malignant disease. It is possible also to get it from dust. But dust of course is very rare in women and particularly so in young women. It is more like miliary tuberculosis than like anything else.

DR. CABOT: There is nothing in particular at the apices, is there?

DR. HOLMES: No; I should say not. There was no evidence of calcification in the glands.

DR. CABOT: No evidence that it started in the lungs?

DR. HOLMES: Of course it is possible that she has glands behind the heart, along the bifurcation of the trachea.

DR. CABOT: I am still inclined to think that it did start in the lungs because of the history. It will be interesting to see what Dr. Mallory says about that.

The generalized tracheal and bronchial râles do not signify anything so near death. They do not increase our suspicion of pulmonary tuberculosis I should say.

My diagnosis is tuberculous meningitis, miliary tuberculosis of the lungs, and if tuberculosis in those places probably miliary tuberculosis

everywhere else. My best guess as to the starting point is the lungs.

BACTERIOLOGIC REPORT

Smear from the pellicle of the second lumbar fluid showed tubercle bacilli.

CLINICAL DIAGNOSES (FROM HOSPITAL RECORD)

Tuberculous meningitis.
Acute miliary tuberculosis.
Bronchopneumonia.

DR. RICHARD C. CABOT'S DIAGNOSES

Tuberculous meningitis.
Miliary tuberculosis of the lungs.
Probably general miliary tuberculosis.

ANATOMIC DIAGNOSES

1. *Primary diseases.*

Miliary tuberculosis involving the lungs, liver, spleen, kidneys, intestines, ovary and lymph nodes.
Tuberculous meningitis.

2. *Secondary or terminal lesions.*

Acute bronchitis.

PATHOLOGIC DISCUSSION

DR. TRACY B. MALLORY: We found miliary tuberculosis and tuberculous meningitis. I do not feel at all sure where the initial lesion was. The lungs showed very slight apical scars. There was nothing which appeared acute enough to be a probable source for the spreading miliary process. There was fairly profuse and generalized enlargement of the mesenteric lymph nodes. On the whole they seemed a more probable source of infection than anything else. We were not able to find ulceration of any single node into a blood vessel or a large lymphatic.

DR. CABOT: Those were caseous nodes, were they?

DR. MALLORY: Some of them were caseous. The majority of them showed fairly fresh tuberculosis without caseation.

CASE 18042

SUDDEN DEATH SHORTLY AFTER A PERIOD OF ACUTE ALCOHOLISM

MEDICAL DEPARTMENT

PRESENTATION OF CASE

DR. ALFRED O. LUDWIG*: This is the case of a man fifty years of age, a Swede, who had done unskilled work in a hospital for many years.

First admission. His first entry was eleven years before his final admission. He had apparently a typical case of appendicitis with perforation. A laparotomy was performed and the appendix was removed. He made an uneventful recovery.

Second admission. His next entry was ten years later. His chief complaint at that time was that he had had sugar in his urine for three weeks.

The history of his illness was as follows. Three weeks before entry he suddenly had fever, headache, back pain and an irritating non-productive cough. He was sent to a hospital by his doctor with a diagnosis of "grippe". He stayed there four days with relief of his symptoms. Urine examination at that time showed the presence of sugar. He was advised to remain for further studies, but preferred to go home. He came here for further treatment. He had been on no diet. One week before entry he went to work and felt well except for easy fatigability. He had had increased thirst during the past three weeks, but no polyuria or polydipsia. Dr. Bauer saw him and sent him to the wards.

In addition he gave a past history of having had gradual onset of constipation and epigastric and lower abdominal tenderness ever since his operation ten years before this. The symptoms had been more severe during the last two years before this second entry. There was a feeling in the epigastrium of discomfort and slight pressure, usually relieved by food. It usually came on when his stomach was empty. It rarely occurred at night and when it did was relieved by a glass of milk, three or four soda mint tablets or a teaspoonful of soda. Food usually helped him most. There was no definite relation of this pain to constipation, but when he was constipated he noted that the pain was more severe. He had been symptom free for two or three days at intervals of two or three weeks. Otherwise his history was essentially negative.

Physical examination at that time showed an obese man in no distress, with wheezy breathing. His teeth were carious. His chest showed moderate increase in the anteroposterior diameter. The chest moved as one piece with respiration. The lower borders of the lungs were prolonged downward. The lungs were slightly hyperresonant. There were audible and palpable rhonchi on inspiration and expiration. The heart was found to be normal. The arteries were thickened but not tortuous or calcified. The dorsalis pedis pulsated well.

He had sugar in his urine.

He had x-ray studies at that time. The teeth showed marginal pockets; no definite abscesses. The lung fields were clear. A chest film was taken as part of the routine examination of a diabetic. A gastro-intestinal series showed a duodenal ulcer on the greater curvature of the duodenal cap. The patient was so fat that it

*Junior interne on the East Medical service.

was impossible to palpate his cap, but the deformity was seen in three positions. The radiologists said they would repeat the examination if the findings did not confirm the clinical picture. The sinuses showed the appearance of sinusitis.

He was started on a diet of carbohydrate 182, protein 78, fat 161. On that diet the twenty-four hour specimen of urine showed 0.6 per cent or 12 grams of glucose. He was apparently working at that time and stayed in the ward at night. He had milk and powders between meals. The note before discharge states that he had no gastro-intestinal symptoms except belching of gas throughout the day. His bowels were regular. His urine showed only a trace of sugar, although his blood sugar was still high, 182, but the diabetes was gradually coming under control. His blood sugar at admission had been 250, I suppose fasting. He was discharged on that diet with a diagnosis of diabetes mellitus, duodenal ulcer, pansinusitis and emphysema of the lungs. In addition to his diet he had powder A after meals and at bed time, and Russian oil.

Third admission. We did not hear from him again until ten months later, when he was brought into the Emergency Ward semicomatose. The only history obtainable was that he had felt well until he refused to stay on his bland diet about two weeks previously. At that time he began to drink bay rum and rubbing alcohol, and for several days drank considerable amounts. Three days before entry he vomited some coffee grounds material. He still continued to feel quite well. Three days before entry he stopped drinking and had had nothing in the way of alcohol since. About seven o'clock the evening of admission he suddenly became comatose. He was seen by a doctor who believed that the patient had perforation of his ulcer. He sent him in to the Massachusetts General Hospital.

He was seen by the East Medical service at midnight. He barely responded to questions.

Physical examination showed a well-developed and obese man in shock. The skin and mucous membranes were pale. The pupils reacted poorly. The tongue was coated and dark brown. The chest was barrel shaped and hyperresonant. There were coarse râles at the bases and bronchovesicular breath sounds. The heart was not enlarged. The action was rapid and the sounds were poor. There was a slight systolic murmur at the apex. The abdomen was negative except that the liver was palpable 4 fingerbreadths below the costal margin. The arm and leg reflexes had disappeared. In addition he had fluctuant suppuration at the left elbow and edema of the shins.

The urine at admission showed a brown test for sugar, with no acetone or diacetic acid. The red blood cell count was 1,720,000, with 40 per cent hemoglobin, Tallqvist. There was a very strongly positive guaiac in both the stool and the vomitus.

It was believed that he was in a state of shock, presumably from bleeding ulcer. Insulin was ordered by test for what was believed to be diabetes. His urine gave a brown test at that time. His blood was grouped, and as his blood pressure fell from 96/65 to 80/60 transfusion was done at about three o'clock in the morning. At five o'clock the blood pressure had again dropped. At 5:25 he died.

DR. GEORGE W. HOLMES: The films show very little variation from normal. There is some increased peristalsis and the duodenal bulb is never well filled. I do not believe we can make a diagnosis from the films alone.

DR. FRANCIS T. HUNTER: Does your father find that illicit liquor today contains considerable amounts of copper?

DR. MALLORY: Yes.

CLINICAL DIAGNOSES (FROM HOSPITAL RECORD)

Duodenal ulcer, bleeding.
Diabetes mellitus.
Obesity.

ANATOMIC DIAGNOSES

Ulcer of the pylorus.
Petechial hemorrhages of the stomach.
Erosions of the esophagus.
Fatty vacuolization of the liver.

PATHOLOGIC DISCUSSION

DR. MALLORY: This is another case very much like the last, Case 18022*, where the autopsy fails to explain the symptoms satisfactorily.

We found at autopsy a stomach filled with coffee grounds material, pretty obviously partially digested blood. We found at the pylorus what was called in gross a very minute erosion, only 3 millimeters in diameter, with no suggestion of any large blood vessels running into it. Microscopic examination however showed that it had eroded through the muscularis mucosa, which is a more or less artificial criterion used to differentiate erosion and ulcer. It was such an extremely tiny ulcer that it is hard to see how it was possible that it could have resulted in fatal hemorrhage. The remainder of the stomach showed very numerous scattered petechial hemorrhages throughout, and the esophagus showed rather numerous erosions.

The one other striking finding was the liver. It was nearly three times normal size. It was extremely pale and filled with fat, a degree of fatty vacuolization that is hardly consistent with mere obesity. We characteristically find this in the early stages of alcoholic cirrhosis. We

*Published January 14, 1932.

could not find any hyalin degeneration, however, to confirm this.

A certain number of cases of acute alcoholism do have severe and fatal hematemesis without cirrhosis apparently as a result of erosions at the cardia and the lower end of the esophagus, perhaps mechanical in origin from excessive vomiting. Weiss has reported several cases from the City Hospital of that character. Usually in cases of that sort death comes on pretty immediately after a drinking spree, not with an interval of several days such as we seem to have here. So that I am not entirely satisfied with that explanation. I do not however feel that this very tiny ulcer could have been the cause of death.

DR. CHESTER M. JONES: We have one other possible cause for the hemorrhage in the presence of rather severe diabetes in the patients who come in with diabetic acidosis. While this was not so severe as some of the cases we see, I wonder if that may have been the cause.

DR. WALTER BAUER: He was a very mild diabetic. He was discharged with a blood sugar of 132 and without any acetone or diacetic acid. He had no evidence of severe acidosis at the time he entered the hospital.

DR. HOLMES: The x-ray examination was a year before his death. Was there no evidence of any scar of an old ulcer?

DR. MALLORY: We found two very small scars, each about 4 millimeters in diameter, on the posterior wall of the duodenum.

DR. HUNTER: Was there no analysis made in relation to poisoning?

DR. MALLORY: No.

DR. HUNTER: Is that a possibility?

DR. MALLORY: I think it is.

DR. FREDERICK T. LORD: Were there any varices?

DR. MALLORY: No. In these cases of hematemesis in acute alcoholism without cirrhosis we do not get varices.

DR. JONES: Would you say this is characteristic of acute alcoholic gastritis?

DR. MALLORY: Not absolutely.

DR. JONES: We have had some in which the abdomen was so tender that it was almost like an acute abdominal condition, such as perforated ulcer. This case was not apparently so severe as that.

DR. HUNTER: The liver might suggest the toxic cirrhosis of an alcoholic.

DR. FULLER ALBRIGHT: If his red cell count was one million he may have had anemia for a long time. He did not get that simply from acute hemorrhage.

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IMPROVEMENT IN THE ELECTRO-CARDIOGRAPH

DR. VANNEVAR BUSH, Professor of Electrical Power Transmission at the Massachusetts Institute of Technology and Dr. William D. Reid, Assistant Professor of Cardiology at the Boston University School of Medicine and Associate Member in Cardiology at the Evans Memorial Hospital have announced (*Technology Review*, January, 1932) an interesting technical improvement upon the string galvanometer employing the thermionic tube widely used in radio engineering, the advantages of this improvement being the complete lack of inertia and the fact that "a significant power output from its plate circuit can be accurately and completely controlled by an extremely small input to its grid". Instead of trying to make the graphic record obtained by this instrument as near like that obtained from the Einthoven string galvanometer, as attempted by others who have used a similar device for indicating small changes of electrical potential, these workers have retained the tracing from the new instrument unchanged, which appears in effect as a magnification of the familiar electrocardiographic tracing, accomplishing, according to Bush and Reid, three things as compared with the old instrument, namely, it has brought out detail, it has avoided errors due to skin current, and thirdly, it has produced an enlarged or magnified record with a relatively fine line.

The value of a technical improvement in a method of recording graphically a physiologic mechanism, clearly will be either in making more widely available the knowledge already obtainable by the method which it supersedes or by extending that knowledge. The essential data obtainable by the present method of clinical electrocardiography, and not otherwise obtainable, are five: (1) the diagnosis of chronic coronary disease especially intraventricular block, (2) the recognition of the effect of acute or chronic infection, toxic agents or deficiency disease upon the heart by the production of auriculoventricular or intraventricular block or alteration of the conduction of the impulse in the muscle indicated by the shape of the record, (3) the diagnosis of occasional instances of acute coronary thrombosis without pain, (4) the elucidation of certain unusual functional disorders of the rhythm (extrasystolic irregularities, auricular flutter) and (5) in revealing a few signs of evil prognostic significance, chiefly low voltage. Whether the more delicate electrocardiograph of Bush and Reid will be less expensive and more sturdy than the present stringed galvanometer and therefore make more widely available this desirable knowledge in cases of heart disease, whether it will add additional data in the study of the cardiac mechanism or alter present electrical theories in regard to the origin and transmission of the cardiac impulse and finally whether the advantage of much increased sensitivity will be offset by distortion of the record due to extraneous current await wide application of this new tool to clinical cases and comparison with the present method.

Of more significance, for the moment, is the example of useful coöperative research between the electrical engineer and the clinical research worker. Chemistry and physics are in their full maturity as practical sciences, contributing largely to the understanding and control of natural phenomena while biology and its child, scientific medicine, great as their practical contributions have been in the last fifty years, are still comparatively in their youth. With the everwidening fields of technical scientific research perhaps the greatest contributions of the future may be born of such associations between workers in scientific medicine and those in the older and as yet more exact sciences.

THE BOSTON MEDICAL LIBRARY

At the annual meeting of the Boston Medical Library the treasurer reported that the income is not sufficient to meet the current expenses and that the membership is not growing.

This brief statement indicates the necessity of more active support by the medical profession throughout the state, for the library is more than a local institution and only a small proportion of the members of the Massachusetts Medical Society are on its roster. With a membership of more than forty-six hundred, the Society should be more generally represented as a supporting body and show the officers who are carrying the burden of administration that it is a privilege to be associated with them.

Publicity has been given to the needs of the library in recent years through the campaign for funds in association with the Massachusetts Medical Society and personal solicitation for members, but competing appeals and unfavorable conditions in the financial situation prevented the attainment of the objective of the last drive.

It may be that it is not generally recognized that this library is one of the great reservoirs of medical literature in the world and maintains the policy of the open door for all who care to examine its treasures and in addition serves as a circulating library for New England. Although it is recognized that present economic conditions prevent generous giving by most people, it seems reasonable to suggest that the campaign for support should be a continuing program within the profession at least, with the hope of an increasing membership and growing appreciation of the opportunity to help a great medical enterprise.

When the governing body may make public its plans, we hope that general support will be forthcoming.

THE TRUE PHYSICIAN

One of the penalties of success, to a person of a naturally retiring disposition, is the prominence which must occasionally be given to his name. This penalty our friend, Dr. Lawrie B. Morrison, master of roentgenology, has now incurred. He might easily owe it to his professional success, which has been great, but others have been successful in that respect in equal measure. It is to his kindliness of heart, his instinct for helpfulness, his capacity for friendship that he now owes the almost public burst of sympathy that has gone out to him in an affliction which is the result of years of service to others.

When the x-ray was in its infancy he became first its servant and then its master but in mastering it he, like so many other of the pioneers, suffered the wounds of battle. His grateful friends and his grateful colleagues, many of whom are also his grateful patients, unite in wishing him a speedy recovery from this latest wound which science has inflicted.

THE AFTERMATH OF THE FITCHBURG SMALLPOX EPIDEMIC

A case of smallpox has been reported from Leominster, Massachusetts which seems to have been an extension from the Fitchburg epidemic.

One person who refused to be vaccinated has been quarantined as a possible menace. The great majority of the people of Fitchburg have been recently vaccinated and this supports the contention that this city is the safest place so far as the danger of smallpox is concerned.

Vaccination has again demonstrated the effective method for stamping out smallpox but unfortunately even this example may not convince the opponents of this preventive practice.

THIS WEEK'S ISSUE

Contains articles by the following named authors:

Henderson, Yandell. B.A., Ph.D. Formerly Chairman, Section of Pathology and Physiology, American Medical Association and Associate Member, American Medical Association. Instructor and later Professor of Physiology, Yale Medical School 1900-1920. Professor of Applied Physiology, Yale University 1920 to date. Consulting Physiologist, U. S. Bureau of Mines 1912-1922, and Chemical Warfare Service 1922 to date, U. S. Army. Member of National Academy of Sciences. His subject is "Reasons for the Use of Carbon Dioxide With Oxygen in the Treatment of Pneumonia." Page 151. Address: Yale University, New Haven, Conn.

Lund, Fred B. A.B., A.M., M.D. Harvard University Medical School 1892. F.A.C.S. President, Boston Surgical Society. Surgeon-in-Chief, Carney Hospital. Consulting Surgeon, Boston City Hospital, etc. His subject is "Colitis Resulting in Obliteration of the Lumen of the Intestine." Page 156. Address: 319 Longwood Avenue, Boston.

Smith, Millard. M.S., B.S., M.D. Harvard University Medical School 1923. Formerly Assistant Professor of Medicine, University of Michigan. His subject is "A Study of 102 Cases of Atrophic Arthritis. II. Constitutional Defects." Page 160. Address: 472 Commonwealth Avenue, Boston.

Davis, Max. A.B., D.N.B., M.D. Harvard University Medical School 1925. Assistant in Obstetrics, Boston University School of Medicine. Assistant in Gynecology, Boston University School of Medicine. Second Assistant Obstetrician, Massachusetts Memorial Hospitals. Gynecologist to Out Patient Department, Massachusetts Memorial Hospitals. Address: 311 Commonwealth Avenue, Boston. Associated with him is:

WALKER, ELISABETH W. B.S., M.A. Address: 311 Commonwealth Avenue, Boston. Their subject is "Modern Laboratory Methods for the Early Diagnosis of Pregnancy." Page 173.

GARGILL, SAMUEL L. M.D. Tufts College Medical School 1925. Assistant in Medicine, Harvard Medical School and Beth Israel Hospital. His subject is "Cinchophen Poisoning. A Report of Three Cases." Page 183. Address: 485 Commonwealth Avenue, Boston.

The Massachusetts Medical Society

STATED MEETING OF THE COUNCIL

A STATED meeting of the Council will be held in John Ware Hall, Boston Medical Library, Wednesday, February 3, 1932, at 12 o'clock, noon.

Business:

1. Reading record of last meeting in abstract.
2. Report of Committee of Arrangements.
3. Report of Committee on Membership and Finance, on Membership.
4. Report of committee appointed to consider a petition for restoration to the privileges of fellowship. Committee to be appointed for another petition.
5. Delegates to be appointed to annual meetings of five New England State medical societies; to the House of Delegates, American Medical Association for the term of two years from June 1, 1932; to the Annual Congress of the American Medical Association at Chicago in February, 1932.
6. Report of the Treasurer for the financial year, 1931.
7. Report of the Auditing Committee.
8. Report of the Committee on Membership and Finance, on Finance, with Budget for the year, 1932.
9. Report of Committee on Public Relations.
10. Reports of other committees.
11. Incidental business.

WALTER L. BURRAGE, M.D.,
Secretary.

Brookline, January 27, 1932.

Councilors are reminded to sign one of the two attendance books before the meeting.

In the interest of accuracy and to help the stenographer, Councilors are requested to state their names and the Districts they represent before speaking from the floor.

DIRECTORY OF THE MASSACHUSETTS MEDICAL SOCIETY, 1932

Error in address: The address of Harry F. Friedman should be 270 Commonwealth Avenue, Boston, as previously, and not 491 Commonwealth Avenue, the new address of Hyman B. Friedman. An error in copying.

Error in first name: Hamon S. Trueman of West Medford, should be Harmon S. Trueman. A typographical error.

Error in middle name and spelling of family name: Abraham Howard Yudelman, of Boston, should be Abraham Harold YuDelman. A perpetuated typographical error, and misspelling.

Page 66. Hale, Jesse Collins, Gardner, 21 Pleasant Street, should be Hales, Jesse Collins, Gardner, 66 Parker Street.

WALTER L. BURRAGE, *Secretary.*

NOTICE TO THE MEDICAL PROFESSION AND TO HOSPITALS IN BOSTON

FOR nine years the Department of Tropical Medicine of Harvard has been offering to perform without charge, on the request of any physician of Boston, a great variety of tests relating to the diagnosis of tropical diseases. Comparatively few of these tests have been called for but the demand for some of them has increased to such a point as to require a good deal of time from members of the Laboratory Staff. Owing to the necessity of curtailing the Laboratory Staff, and in order to defray the expense incidental to making the examinations called for, the Department feels that a charge should now be made to such patients as may be able to pay.

The Department, however, has no machinery for the collection of fees and, therefore, it proposes that after February 1, 1932 all hospitals or private physicians requesting examinations *make a charge of five dollars ($5) for each such examination to patients that can afford to pay it, and that sums so collected be turned in to the Department of Tropical Medicine at the end of each month.* Checks should be made payable to The Department of Tropical Medicine of Harvard University and mailed to Miss C. M. Casassa, Building D I, Harvard Medical School.

When patients are unable to pay for hospital or private care, the Department will be glad to make its examinations free of charge.

The Department is prepared at nearly all times to perform examinations of feces for protozoa or helminths and to make and to examine blood smears for malaria. Other tests will be performed, hereafter, by special arrangement only.

Please kindly make inquiries of Miss Casassa, Secretary of the Department and make arrangements for tests through her. The telephone number is that of the Medical School, Regent 2380.

Signed: GEORGE C. SHATTUCK,
For the Department of Tropical Medicine
of Harvard University.

January 18, 1932.

PHYSICIANS' OPINIONS ON THE INFANTILE PARALYSIS SERVICE OFFERED IN 1931*

BY GEORGE H. BIGELOW, M.D., AND HAROLD W. STEVENS, M.D.

EVER since the epidemic of anterior poliomyelitis in 1916 the Harvard Infantile Paralysis Commission has to a varying degree been offering diagnostic and convalescent serum service to the physicians of the State. Realizing the importance of this work, the Department of Public Health has been coöperating in this service and of late years has made small financial contributions. Last summer and fall with the increased number of cases His Excellency the Governor made an emergency appropriation of $10,000 toward this work. Within a week the number of consultants had been expanded from two until they reached the maximum figure of sixteen and machinery was started for collecting convalescent serum which eventually totaled more than 100 litres.

Now the Department is interested in considering what, if any, part in this service it should continue to take. As a guide in its decision letters and attached questionnaires were sent to 493 physicians who our records showed used this service. To date 273 have replied. The total cases of anterior poliomyelitis reported for 1931 were 1428. Through this service, offered only on call of physicians, over 1000 patients were visited. Of these at least 700, or half of all the cases of the disease in the State, had poliomyelitis. Of these, 543 were cases of the disease in the "pre-paralytic" stage and were given convalescent serum. Information on the final outcome of these treated cases is still in process of collection and compilation. To the 493 physicians using the service the following letter and questionnaire were sent:

"To Physicians using Infantile Paralysis Service:

"Dear Doctor:

"Under an emergency appropriation from His Excellency, Governor Ely, and in coöperation with the Harvard Infantile Paralysis Commission, diagnostic and serum service was offered during the recent outbreak. With the Commission we are now considering the future of such service. In view of economic restrictions, the drain of such service on investigative resources, and the like, such reconsideration of the matter at this time is imperative.

"Our records show that you utilized this service. We are particularly anxious to obtain what suggestions you may have for more satisfactory methods of convalescent serum distribution. The available supply of such serum is always extremely limited, so that it cannot be distributed as freely to physicians as are other biological products. Also, as its value is still under investigation, further data as to its efficacy should be collected. For this reason this serum has been distributed by the Commission and not this Department. We all wish to make the serum as quickly available as possible consistent with the limited supply. We would therefore particularly appreciate suggestions from you as to better methods of distribution, which would make the serum available when and where needed, without taking the case away from the care of the family physician. With this in mind we would appreciate your answering the attached questions in as much detail as you are willing.

Yours truly,

(signed) GEORGE H. BIGELOW, M.D.,
Commissioner of Public Health."

"1. Was the poliomyelitis consultation and serum service as offered you this year satisfactory?
2. If not, what defects should be corrected?
3. Would you wish to have the service, including serum distribution, continued on the same basis in future years, viz., consultation service offered free to physicians through the Commission with distribution of serum only through the Commission's consultants?
4. Would you prefer that a local consultant be appointed by the local county or district medical society, the serum to be available only at the discretion of this local consultant?
5. If neither of these plans is satisfactory, what plan for serum distribution, consistent with the limited supply of serum available, would you suggest?

Name .....
Address ....."

The response to these questions was gratifying. One possibly significant comment upon the response is the fact that no return envelopes accompanied the letter. Brief summaries of the replies are set forth in the appended table.

Every response brought some reply to the question whether the service was satisfactory. 267 physicians answered "Yes"; 6 answered "No". Of the 267 answering "Yes" more than one-third said it with special emphasis. Of the six negative replies, one was stated as follows: "No; I would like to have larger doses used and more consultations than was possible." Four of the negative replies seemed related to unfortunate incidents that were perhaps inevitable to service on so large a scale. One "No" was accompanied by a thoughtful and cogent criticism of some of the defects of the service.

To question 2, regarding faults to be corrected, the reply "None", together with the blanks representing no replies, account for over 200 of the returns. Among specific criticisms mentioned, the largest group, 14 in number, referred to delay in getting consultation and serum. Several mentioned the implications of "state medicine". Some suggested more experienced and permanent consultants. A few were disturbed by the possible humiliation of family physicians.

Question 3 asked for opinions upon the con-

*From the Massachusetts Department of Public Health.

tinuation of a similar service. This question brought a total of 248 replies. 235 said "Yes"; 13 said "No". Of the 235 affirmative replies, 13 added special emphasis. The 13 negative replies were not amplified.

Opinions upon the desirability of locally appointed consultants came from 223 physicians. 39 said "Yes"; 184 said "No". Of those who said "Yes" 4 added special emphasis. Of the negative replies, 24 were especially emphatic. Several "No's" were recorded in large capital letters or in words that conveyed an equivalent impression.

Question 5, asking for suggestions upon plans different from that under trial, brought no reply from 121 physicians; 84 more recorded "None". Among the concrete suggestions offered, the largest number, 8, proposed consultation and serum service from hospital centers. Five suggested local consultants for remote districts. A few suggested that serum be distributed upon the telephone report of a positive diagnosis by the family physician; a few suggested that the family physician be left to handle his problems according to his own judgment.

A number of detailed replies do not permit of classification. They gave valuable suggestions, however. Also, there were weaknesses in the service of which we were aware that were not brought out in any of the replies.

A summary of the replies to questions 1, 3 and 4, grouped according to counties and also for the entire state, is as follows:

	Physicians Replying	(1) Service Satisfactory		(3) Continue Service		(4) Local Consultant	
		Yes	No	Yes	No	Yes	No
Barnstable	7	7	—	7	—	1	5
Berkshire	8	8	—	8	—	—	6
Bristol	9	9	—	8	—	2	7
Essex	31	30	1	29	1	7	21
Franklin	8	8	—	7	1	1	7
Hampden	53	52	1	38	4	13	29
Hampshire	29	28	1	24	2	2	18
Middlesex	51	50	1	44	2	4	36
Norfolk	17	16	1	16	—	3	11
Plymouth	8	8	—	7	1	1	7
Suffolk	26	26	—	24	—	1	18
Worcester	26	25	1	23	2	4	19
Totals	273	267	6	235	13	39	184

(No replies were received from Dukes or Nantucket Counties.)

SUMMARY

In summary, 273 physicians, out of 493 using the service, replied. Of these, 267 found the service essentially satisfactory. Six did not. 235 desired it continued essentially as it was given last summer, 13 desired some change. 39 preferred a local consultant, presumably appointed by the local medical societies; 184 preferred not to have local consultants. These comments will be of great value in helping the Department plan its work in this field for the future.

THE BOSTON MEDICAL LIBRARY

ANTONJ VAN LEEUWENHOEK
1632-1723

CONSIDERING the important rôle that the microscope has played in the study of Natural History and of the art of medicine it is certainly quite surprising to find so little reference in the literature to the life history of the man who played a significant part in the development of the instrument and made so many contributions to the science of microscopy as did Leeuwenhoek. He sent over 300 papers and letters to the Transactions of the London Philosophical Society and 27 to the Paris Academy of Sciences and yet apparently, until comparatively recent times, no one has written a biographical sketch of his life, except Dr. Carpenter, who has compiled a very meagre one for the Encylopedia Britannica. It is certainly true that he was not by training a scientist but where he acquired the keenness of observation that characterized his use of the instrument with which his name is connected in history is not apparent. He was born in Delft on October 24, 1632 and died in the place of his birth 91 years later, on August 26, 1723. After the usual schooling of a youth of his time he was given employment in the linen draper's establishment of a relative in Amsterdam. Here he remained a few years, becoming the accountant for the house before he gave up that business and returned to his native town of Delft, at the age of 22, where he married and settled down for the rest of his life. His father died early in van Leeuwenhoek's childhood, apparently with the expectation that the young man would follow his forebears in the brewery business. He came from good Dutch, burgher stock and it would appear that he had sufficient means to permit devoting himself to his major interests, for neither of the occupations to which there is any record of his having been devoted, viz., that of a linen draper in the capacity of an accountant, or that of a chamberlain, or Beadle, to the Sheriff of Delft, could possibly have provided for his physical needs and those of his family of a wife and five children. Just how early he developed his interest in the construction of microscopical lenses is not known, nor how long he served in the linen draper's shop and it is only conjecture that he must have oc-

cupied his spare time in acquiring the art of making lenses during this period of apprenticeship. Shortly after his return to Delft he was appointed by the town authorities to the office of Beadle which he held for 39 years and for which service he received an emolument equivalent to about one hundred dollars per annum. The duties were not confining nor arduous, which doubtless accounts for his being able to devote so much time to his avocation. He soon demonstrated that single, short-focused lenses were superior to the compound ones that were in vogue in his day, for the magnifying power of glass and quartz had already been demonstrated by the Jansens and many others prior to the middle of the seventeenth century. Roger Bacon (1267) refers to the fact that globes of glass had been employed for magnification. Another Englishman, Digges, had used lenses for magnification in 1571 and the Hollander, Zacharias Jensen (1590), had been prominent among the earlier manufacturers of lenses for this purpose. In the opinion of Charles Singer the one who demonstrated the usefulness of the microscope was Galileo who perfected a magnifying lens for the study of the "infinitely small" at the same time that he made his first telescope, viz., about 1608. All the work of grinding the lenses and making the standards Leeuwenhoek did. He is said never to have sold any of the instruments he made though he gave a few away, but he always obstinately refused to tell how he ground his lenses or of what materials he made them. In all, he appears to have produced over 400. To the Royal Society, which was frequently insistent that he divulge his secrets, he was always evasive in his answers, if indeed he made any answer at all. When he was old, Liebnitz besought him to teach certain young men the art he had perfected but he declined, saying that no young man would give the time that was necessary to acquire the skill. He did present the Royal Society with 26 microscopes but they have disappeared since 1740. These had varying magnifying powers, up to 160 diameters. His knowledge of how to design a lens must have been acquired in some other way than by any knowledge of physics or mathematics, for his schooling was of the most elementary sort. He was acquainted with only the language of his native tongue, so he could not have acquired knowledge of such subjects from his reading.

In 1668 he extended Malpighi's observations upon the capillary circulation and six years later described the red corpuscle in the human subject which had already been noted by Swammerdam, comparing its shape with the more ovoid contours of these same corpuscles in the frog. This in itself should have entitled him to sufficient distinction to merit a biography. When one of his pupils, Hamm, and later Leeuwenhoek himself, identified the spermatozoon, it certainly would have been no more than justice for someone to have commented upon the fact that a notable discovery had been made. Leeuwenhoek reported the results of his studies on this subject in 1677. He made observations upon the crystalline lens, striped muscle and the teeth and was the first to recognize the spores of yeast. Everything was grist for his mill and he extended his work into the botanical field, establishing differences in the microscopic appearances of the stems of mono- and dicotyledenous plants. As if these observations were not enough to identify him with progress in the scientific field he is credited with having shown, by a drawing in one of his works, the earliest representation of a bacterium. He apparently owed his success to his indefatigable energy and insatiable thirst for knowledge. His writings are only records of his observations though he was led by them to carry on experiments to confirm the things he saw. For forty years he appears to have plodded along in this way until his friend, Regnier de Graaf, persuaded him to send his first communication to the Royal Society. This was entitled "Specimens of Observations made by means of a Microscope invented by A. Van Leeuwenhoek in Holland." This was in 1673. In 1680 he was elected to Fellowship in the Royal Society and a steady stream of papers from his pen found their way to London during these seven years. It has been said by some commentators that he was a physician but there is nothing in his writings, or in any account of his life, to indicate that he ever had any affiliations with the study or practice of that profession. He was immensely interested in natural history and the East India Company frequently sent him specimens of this nature. In 1698 Peter the Great paid him a visit to inspect his microscope and learn of its revelations. In view of the results that grew out of the studies which his instruments made possible it is interesting to note that William Harvey was 54 years old when Leeuwenhoek was born and had probably already published the results of his investigations upon the circulation of the blood. Confirmation of what Harvey had discovered was to be established by Malpighi and Leeuwenhoek when they were able to study the circulation in the tadpole's tail and elsewhere. Leeuwenhoek did not, as certain writers have claimed for him, discover the red blood corpuscle. That was done, before his observations, by Swammerdam, but he did succeed in demonstrating the flow of blood through the vessels in the bat's wing, the tadpole's tail, the cock's comb and the rabbit's ear. He also advanced theories as to the cause of the color of the blood and suggested that the exchange of impurities accumulated in the blood stream was effected at the point where he had observed the

arteries to merge into the veins. His opinion was that the vessels in the creatures he studied were calibrated to the size of a single red corpuscle and that it was necessary that this should be so in order that the distribution of the nutriment supplied to the tissues should be evenly adjusted. He even carried out mathematical calculations based on this conception of the calibration of vessels by which he determined the length of time that would be required to carry away a clot of a certain size and restore to normal the circulation in the ruptured vessel. In addition to his more important observations, to which reference has already been made, he investigated the brain substance, differentiating the gray and the white areas. He showed the squamous nature of the outer layers of the skin, comparing it with the epithelial cells of the surface of the tongue. He apparently was the first to describe certain of the protozoa, viz., the rotifers and the foraminifera. In fact he may very properly be regarded as a pioneer in the study of histology though his pioneering led him nowhere. His lack of education and scientific imagination prevented his being more than a recorder of observations which he made no attempt to employ in any synthetic way as would a man of another kind of genius. He apparently possessed that attribute which someone has offered as a definition of genius, i.e., the capacity of "taking infinite pains", but he lacked that quality of mind which would have enabled him to make much more of his opportunities. If he and Pasteur, for example, could have changed places what a different start histology, and perhaps pathology, might have had. The record which he has left behind in his written work is a chaotic mass of observed facts, but they *are* facts and it was probably greatly to his credit that with his mental equipment he did not attempt to do anything more than observe and record. In an age when "spontaneous generation" or abiogenesis, was the theory upon which the presence of life upon the earth was explained most satisfactorily, it is interesting to note that what Leeuwenhoek had learned from his microscopical investigations had made that theory untenable to his mind, for he writes that he "holds it equally impossible for a small shell fish to be produced without generation as for a whale to have its origin in the mud".

It does not appear that Leeuwenhoek ever traveled. Indeed there is no record that he left his native city of Delft after he came back from Amsterdam when he was twenty-two. He had a good friend in de Graaf who, recognizing the value of his work, was probably responsible for its being made the common property of the scientists of that day, by getting his observations recorded before scientific bodies. It was in gratitude to the Royal Society of London for the title with which they honored him, that he sent them a cabinet containing the twenty-six microscopes which have since been lost. He lived to a ripe old age and kept his interest in the studies which had occupied his earlier years, close up to the time of his death. He was buried in the Oude Kerk in his beloved Delft, along with two other of his distinguished countrymen, Grotius, the theologian and Van Tromp, the famous Dutch admiral. The monument marking the place of his burial was erected, not by his fellow citizens or foreign admirers of his genius but, as the inscription reads: "This monument is erected to her very dear father by his sorrowing daughter, Maria a Leeuwenhoek."

Samuel Hoole (1798) who first collected and translated into English the works of Leeuwenhoek apparently made no attempt to secure biographical data but was content to let his works speak for themselves. Delft, the town of his birth and the scene of his activities, was a thriving community but apparently was too busy with its commercial pursuits to have been conscious of the genius it was harboring, and though the authorities made him the incumbent of an inconsequential municipal office which he occupied for a long period and from which he received the salary until his death, it was the neighboring city of Amsterdam which tardily recognized the great value of the work he had done for science and was the provider for and awarder, once in ten years, of a prize to the one who contributes most, in that period, to the science of microscopy.

To those who may be interested in following up the work of this remarkable man the following are a few of the sources of information to which reference may be made:

In 1798-1801 Samuel Hoole published, in London, a two-volume collection of Leeuwenhoek's more important communications to the Royal Society of London and the French Academy, in both of which he had been honored by membership. Haaxman in 1871 and Harting in 1876 published memoirs of his life. C. Dobell, in Parasitology, Vol. 15, pp. 314-319 (1923), gives a brief account of his life work and there states that if one really desires to get an idea of the character of the man he must go to the originals in the Dutch language, as the English, French and German writers on the subject of his life are full of inaccuracies.

H. G. Plimmer, Presidential address (Apr. 16, 1913) before the Royal Microscopical Society, entitled "Bedellus Immortalis," published in part 2 of the 1913 *Journal of the Royal Microscopical Society*. (April 1913.) L. B. Becking, Vol. XVIII, No. 5, pp. 547 of the *Scientific Monthly*. Benj. W. Richardson in the Disciples of Aesculapius Vol. I, pp. 108. W. A. Locy, The Growth of Biology, 1925. D. F. Harris, *Scientific Monthly*, Vol. 12 (1921), pp. 150-160.

MASSACHUSETTS LEGISLATIVE NOTES

HOUSE 203—The date for hearing on this bill, originally assigned for January 26, has been changed to February 9 in room 481 at 10.30 before the Committee on Education.

SENATE 106—An Act providing for the Establishment and Maintenance of a State Hospital for the Care of Nervous Cases.

Be it enacted by the Senate and House of Representatives in General Court assembled, and by the authority of the same, as follows:

SECTION 1. The department of mental diseases is hereby directed to establish in such city or town as it may, with the approval of the governor, determine, a state hospital for the care of nervous cases. For such purposes and with like approval the department may acquire by purchase or take by eminent domain under chapter seventy-nine of the General Laws land suitable for a site therefor and erect thereon all necessary buildings, and may furnish and equip the same.

SECTION 2. Section five of chapter nineteen of the General Laws, as most recently amended by section two of chapter four hundred and three of the acts of nineteen hundred and thirty, is hereby further amended by striking out, in the last, the word "and" and inserting in place thereof a comma, and by inserting after the word "school", in the same line, the words:—and the hospital for nervous cases,—so as to read as follows:—*Section 5.* The boards of trustees of the following public institutions shall serve in the department: Belchertown state school, Boston psychopathic hospital, Boston state hospital, Danvers state hospital, Foxborough state hospital, Gardner state colony, Grafton state hospital, Walter E. Fernald state school, Medfield state hospital, Metropolitan state hospital, Monson state hospital, Northampton state hospital, Taunton state hospital, Westborough state hospital, Worcester state hospital, Wrentham state school and the hospital for nervous cases.

SECTION 3. Section twenty-five of chapter one hundred and twenty-three of the General Laws, as most recently amended by section three of said chapter four hundred and three, is hereby further amended by inserting after the word "hospital" in the next to the last line the words:—, the hospital for nervous cases,—so as to read as follows:—*Section 25.* The state institutions under the control of the department shall be Worcester state hospital, Taunton state hospital, Northampton state hospital, Danvers state hospital, Grafton state hospital, Westborough state hospital, Foxborough state hospital, Medfield state hospital, Monson state hospital, Gardner state colony, Wrentham state school, Boston state hospital, Walter E. Fernald state school, Boston psychopathic hospital, Belchertown state school, Metropolitan state hospital, the hospital for nervous cases, and such others as may hereafter be added by authority of law.

SECTION 4. The trustees or superintendent of said hospital may receive therein as a boarder and patient any person desirous of submitting himself for observation or treatment and who makes, by himself or a member of his family, or other suitable person, application for admission. No such person shall be detained in said hospital more than three days after having given written notice of his intention or desire to leave the same.

SECTION 5. The provisions of chapter one hundred and twenty-three of the General Laws applicable to voluntary patients in the institutions under the supervision of the department of mental diseases shall, so far as apt, apply to patients in said hospital for nervous cases.

SECTION 6. Of the appointments of trustees of the state hospital for nervous cases which shall be originally made by the governor, with the advice and consent of the council, under authority of this act, in January, nineteen hundred and thirty-three, one shall be for a term of one year, one for a term of two years, one for a term of three years, one for a term of four years, one for a term of five years, one for a term of six years and one for a term of seven years, from the first Wednesday in February, nineteen hundred and thirty-three, subject, however, to the provisions of section six of chapter nineteen of the General Laws.

SECTION 7. Until the appointment and qualification of trustees as aforesaid,

(1) The state hospital for nervous cases shall be directly under the control of the department of mental diseases in accordance with the provisions of section three of chapter one hundred and twenty-three;

(2) Said department shall have and exercise all the powers and duties in respect to said hospital which the trustees of the several state hospitals under the control of the department of mental diseases have and exercise in respect thereto, and, in respect to such hospital, shall be subject to all provisions of law applicable to trustees of such state hospitals; and

(3) Said department shall appoint to and may remove from the service of such hospital:

(a) A superintendent, who shall be a physician and shall reside at the hospital, and, with the approval of said department, shall appoint and may remove assistant physicians and necessary subordinate officers and other persons; and

(b) a treasurer, who shall give bond for the faithful performance of his duties.

HOUSE 264—On petition of Armand C. Bang and Gilbert W. Haigh was heard January 20. The purpose of this bill is to create a department of public medicine and health to take over the activities of the Departments of Public Health and Mental Diseases and certain activities of the Departments of Public Welfare and Industrial Accidents. This is in accordance with the contention of Dr. Haigh that the public should be served by a state organiza-

tion comparable to that of the United States Army and Navy medical service.

HOUSE 226—Under the initiative petition of Peter J. Donovan and others for the establishment of a board of examination and registration to regulate the practice of chiropractic. This sets forth the usual method adopted by the Legislature in establishing a board of examination and registration.

HOUSE 284 — Under the petition of Samuel B. Woodward of Worcester and Edward J. Kelley of Worcester requires vaccination of children in private schools and reads as follows:

Chapter seventy-six of the General Laws is hereby amended by striking out section fifteen and inserting in place thereof the following:—

SECTION 15. An unvaccinated child shall not be admitted to a public or private school except upon presentation of a certificate signed by a registered physician stating that he has, at the time of giving the certificate, personally examined the child and that he is of the opinion that the physical condition of the child is such that his health will be endangered by vaccination. The said certificate shall state the reasons for the opinion of the physician who signs it. A child from a household where a person is ill with smallpox, diphtheria, scarlet fever, measles, or any other infectious or contagious disease, or from a household exposed to contagion from any such disease in another household, shall not attend any public school during such illness or exposure until the teacher of the school has been furnished with a certificate from the local board of health, or from the attending physician, stating that danger of conveying such disease by such child has passed.

HOUSE 538—An act regulating the conduct of physicians which reads as follows:

SECTION 1. A physician shall not remove any limb or organ of the body from a patient, without first obtaining consent of such patient, if the patient is mentally and physically capable of giving such consent; otherwise he shall obtain the consent of the patient's husband or wife or nearest available relative or of the patient's parents or guardian. If the patient is unconscious, whereby he could not or cannot know of any necessary operation, and no relative, husband or wife or guardian is within call, the physician may proceed upon his own judgment, if it is necessary to so do for the patient's safety.

SECTION 2. After the removal of such organ or limb the physician shall explain to the patient and husband or wife and relatives or guardian that it is their right to view the part removed from the body, alone, or in the presence of any physician they may choose, and he shall give them a full explanation, alone, or in the presence of any physicians they may choose, as to the necessity of such removal. The physician shall also deliver a written statement of explanation to the patient or patient's husband or wife, or relatives or guardian telling the nature of the operation which he has performed upon the patient and giving his reasons for considering such an operation necessary.

SECTION 3. Upon the completion of an operation by a physician involving the removal of a limb or organ, a physician, other than the operating physician, to be designated by the superintendent or other person in charge of the hospital where the operation was performed, shall take immediate charge of the limb or organ removed and seal said limb or organ in a preservative and lock it away. Said limb or organ so preserved shall not be tampered with, until it is known whether or not the patient or the patient and his relatives wish to take advantage of the right to view said limb or organ.

SECTION 4. A physician shall not, without first obtaining permission from the patient if an adult, or from the patient's parents or guardian if a child, tear or cut by hand or instrument any part of the body, or insert instruments in any part of the body, whereby the patient's rights as a free and sane individual are violated.

SECTION 5. A physician violating any provision of this act shall be punished by a fine of not less than fifty or more than five hundred dollars, or by imprisonment for not more than one year, or by both such fine and such imprisonment.

HOUSE 371—By Mr. Goulart of New Bedford, petition of Arthur Goulart and John Halliwell that persons charged with operating motor vehicles while under the influence of narcotic drugs or intoxicating liquors be granted immediate examination by their own physicians. Legal Affairs.

SENATE 90—To accompany the petition of James G. Moran for legislation relative to the registration and certification of certain persons as chiropodists. Public Health.

HOUSE—NO. 333

By Mr. Brown of Billerica, petition of A. Warren Stearns for an investigation by a special commission relative to the establishment of a new hospital for the criminal insane. Public Welfare.

Resolve providing for an Investigation relative to the Establishment of a New Hospital for the Criminal Insane.

SENATE—NO. 57

To accompany the petition of Carl A. Lindquist for legislation relative to the registration of embalmers. Public Health.

An Act relative to the Registration of Embalmers.

HOUSE—NO. 401

Final Report of the Department of Public Welfare Relative to the NUMBER AND CARE OF CRIPPLED CHILDREN.

HOUSE—NO. 262

By Mrs. Barrows of Melrose, petition of Leslie B. Cutler, for the Massachusetts Civic League, that local public health officers or agents be examined

and licensed by the Department of Public Health. Public Health.

An Act providing for Examining and Licensing Local Public Health Officers or Agents.

HOUSE—NO. 251

By Mr. Prendergast of Boston, petition of William P. Prendergast relative to appointment and fees of physicians who make examinations under the laws relating to compensation for industrial accidents. Labor and Industries.

An Act relative to the Appointment and Fees of Physicians for making Examinations under the Workmen's Compensation Law.

HOUSE—NO. 253

By Mr. Levins of Boston, petition of Marcus J. Levins that compensation of employees injured in industrial accidents be paid from the day of the injury. Labor and Industries.

An Act relative to Fixing the Time when Compensation shall be paid under the Workmen's Compensation Law.

HOUSE—NO. 567

An Act making a Further Appropriation for the Employment of Additional Persons as a Measure of Relief during the Present Unemployment Emergency and for the Further Elimination of the Mosquito Nuisance.

HOUSE—NO. 539

An Act prohibiting the Sale of Patent Medicines containing More than Six Per Cent. Alcohol except upon Prescription of a Physician.

HOUSE—NO. 535

An Act requiring the Restraining of Dogs infected with Disease.

SENATE—NO. 103

An Act regulating the Recovery of Compensation for a Hernia, under the Workmen's Compensation Laws.

HOUSE—NO. 477

An Act authorizing the City of Boston to Borrow Money for Hospital Purposes.

SENATE—NO. 112

An Act enlarging the Scope of the Definition of "Pasteurized Milk."

MISCELLANY

AN EXPEDITION TO GUATEMALA

Under the leadership of Dr. George C. Shattuck a group of physicians embarked on a steamer of the United Fruit Company January 23, 1932, for Guatemala.

The expenses of this expedition will be met by a grant from the Carnegie Institute. This group in addition to Dr. Shattuck consists of Dr. William Curth, Dr. B. L. Bennett, Dr. J. L. Bremer and Carlos Sanchez all from the Department of Tropical Research of the Harvard University Medical School.

KNIGHTHOOD CONFERRED ON DR. HENRY S. WELLCOME

In recognition of his generous support of medical research, Dr. Henry S. Wellcome, of London and Washington, was recently knighted by King George and his name included in the New Year's Honors List.

Dr. Wellcome is of American birth and is widely known in the United States. For years he has been recognized as a leader in research in medical science, and is now serving as the Honorary President of the American Pharmaceutical Association.

It is interesting to note that Dr. Wellcome is a native of Wisconsin and became a British subject by naturalization.

He was graduated at the Philadelphia College of Pharmacy and Science, and from the beginning of his career Dr. Wellcome made original scientific research and strictly ethical methods the foundation of his life's work.

Dr. Wellcome's American interests are wide and varied. He is a Director of the Gorgas Memorial Institute of Tropical and Preventive Medicine, Washington, which operates scientific laboratories at Panama for research work touching causes and prevention of tropical diseases.

Dr. Wellcome is a life member of the American Pharmaceutical Association and has taken an active interest in its scientific work since the beginning of his membership in 1875, and has advocated the establishment of a national headquarters building for the Association in Washington to be known as the "American Institute of Pharmacy." Dr. Wellcome's interest in this project has been evidenced by words and deeds. At the last annual meeting of the Association held in Miami, Florida, during July, 1931, Dr. Wellcome was elected Honorary President of the American Pharmaceutical Association.

DIPHTHERIA COMMISSION ENDS WORK

During the three years of the Diphtheria Prevention Commission's work in New York, under the chairmanship of Thomas W. Lamont, the deaths from diphtheria have dropped by 1,400, and the cases by 17,000. The saving effected by the campaign has been estimated at $3,400,000, as against an expenditure by the commission of $420,000. Of this money, $210,000 was supplied by the city, $190,000 by the Milbank Memorial Fund, and $20,000 by the Metropolitan Life Insurance Company. The work of diphtheria prevention has now been taken over entirely by the Health Department.

ANNOUNCEMENT

Moses Akin, M.D., 94-13 Boulevard, Rockaway Beach, N. Y., has left for Vienna to specialize, on January 23 on the Europa.

CORRESPONDENCE

DOES THE PRESENT ECONOMIC CONDITION REQUIRE REDUCTION OF THE DUES OF THE MASSACHUSETTS MEDICAL SOCIETY?

11 Fairview Terrace,
West Newton, Massachusetts,
January 17, 1932.

To the Editor of the *New England Journal of Medicine*,

Wages are being reduced. Salaries also are being cut. Commodity prices are down. Some hope that fees of doctors, dentists, lawyers will be reduced in the belief that a lower basis will result in the greatest good to the greatest number.

If through the advocacy of the *New England Journal of Medicine* such a condition is hastened, we would expect the assessment dues of the Massachusetts Medical Society also to be reduced. What is the position of the *Journal* on these questions?

FRANK M. SHERMAN.

EDITORIAL NOTE: We hope that nothing has appeared in an editorial in this *Journal* which will hasten the reduction of reasonable fees charged by physicians. We believe that as a rule there is no ground for criticism of charges for services by doctors and we have not learned of any organized movement which is designed to reduce or regulate such charges.

The annual dues assessed by the Massachusetts Medical Society are determined by the Council and do not seem to be excessive in comparison with those of other states.

LEGISLATIVE PROCEDURES RESPECTING THE BILL FOR THE REGISTRATION OF CHIROPRACTORS

The Massachusetts Medical Society
Committee Room
8 The Fenway, Boston, Mass.
Telephone: Kenmore 2094

January 25, 1932.

Editor of the *New England Journal of Medicine:*

The signatures of 20,000 voters were obtained by persons favoring the creation of a Chiropractic Board, no more than 4,000 residing in one county.

This petition was filed, according to the law, with the Secretary of State before the first Wednesday of December, 1931. This petition (initiative) is now known as House 226 and is "An Act Establishing a Board of Examination and Registration to Regulate the Practice of Chiropractic."

House 226 will be heard before the Committee on State Administration but the date as yet has not been assigned. The law requires that the report after a hearing on an initiative petition must be signed by the members of the Committee, giving their reasons for or against in detail. A majority or a minority report may be filed. If the House and Senate report favorably and the Governor signs the bill it becomes a law. If the bill receives an adverse report and is defeated in the House or Senate the petitioners are obliged to obtain 5,000 new signatures before the first Wednesday in August, and deposit same with the office of the Secretary of State, in order to have the initiative placed on the ballot for the State election in November.

We must uphold the present single standard and every member is urged to interest himself and his patients that House bill 226 may be defeated.

Sincerely yours,
THOMAS J. O'BRIEN, M.D.,
For the Committee on State and
National Legislation.

RECENT DEATHS

GILMAN—CHARLES SLEEPER GILMAN died at the Laconia, New Hampshire, hospital January 20, 1932, following a surgical operation.

He was a Fellow of the Massachusetts Medical Society and formerly practiced in Melrose, Massachusetts, and in Suncook, New Hampshire.

He served with the British Army Medical Corps in charge of a hospital previous to 1918 and subsequent to that date joined the Medical Corps of the United States Army. He was Commander of the local organization of the American Legion.

LAVALLEE—GEORGE OMER LAVALLÉE of 790 Merrimack Street, Lowell, died January 13, 1932. He was a native of Lowell, the son of the late Jules and Marie (Lacouture) Lavallée. His premedical education was acquired in the St. Joseph's Parochial School of Lowell and he took the A.B. degree from Ottawa University.

His M.D. degree was conferred by the Harvard University Medical School. Thereafter he engaged in practice in Lowell. He is survived by a wife, Emma (Lucas) and eight children. He was a member of the Massachusetts Medical Society serving as censor in the Middlesex District Society, and also of the American Medical Association. He served on the staff of the Lowell Isolation Hospital and as school physician for more than thirty years and formerly was a member of the Staff of St. John's Hospital.

During the late war he was medical examiner for the Exemption board. He was prominent in several civic organizations.

FRANKEL—DR. DAVID ISRAEL FRANKEL died January 23, 1932 in Boston. He was born in Russia in 1884 and in addition to his registration in Massachusetts he was licensed to practice in Porto Rico, the Bahamas, Florida, and Rhode Island.

He received his M.D. degree from the Boston University School of Medicine and later became assistant visiting surgeon to the Massachusetts Memorial Hospitals and instructor in clinical surgery at the Boston University School of Medicine.

Dr. Frankel was a member of the Massachusetts Medical Society.

He was a student of the Spanish language and while in Porto Rico was associated with the Commissioner of Health.

He leaves a brother, Herbert Frankel, of Framingham, Mass.

OBITUARY

RESOLUTIONS ON THE DEATH OF DR. WALTER EVERARD PAUL

Whereas, in the death of Dr. Walter Everard Paul on July 24, 1931, the Boston Society of Psychiatry and Neurology has lost one of its outstanding members—its president in 1915, a man of sterling qualities of heart and mind, kindly in all his social relationships and ardent in his professional activities, be it

Resolved, that this Society, appreciative of his qualities both as a neurologist and genial colleague, places on record a deep sense of its loss and its recognition of his sterling character and attainments, and be it further

Resolved, that the Society of Psychiatry and Neurology extends to the members of his family its heartfelt sympathy and that these resolutions be communicated to them, be printed in the *New England Journal of Medicine* and inserted in the records of this Society.

(Signed) E. W. Taylor.

December 17, 1931.

NOTICES

CHANGE OF DUTY AND STATION OF COMMISSIONED OFFICER OF THE UNITED STATES PUBLIC SERVICE IN NEW ENGLAND

Surgeon M. V. Veldee has been directed to proceed from Washington, D. C., to Boston, Mass., and to such other points in the State of Massachusetts, and return, in connection with field studies of scarlet fever.

MEDICAL CLINIC AT THE PETER BENT BRIGHAM HOSPITAL

At 3:30 P. M., on Thursday, February 4, in the Amphitheatre of the Peter Bent Brigham Hospital, a medical clinic will be given by Dr. Henry A. Christian, to which physicians are cordially invited. The clinics will be held regularly on Thursday afternoons.

MASSACHUSETTS DEPARTMENT OF EDUCATION

University Extension Course

Keeping Mentally Fit

Gardner Auditorium, State House, Boston

Opening meeting: Monday, February 1, 1932, at 7:45 P. M.

Eight weekly lectures. One semester hour.

Charge: $4 for auditors; $5 for credit students; text extra.

Course leader: Henry B. Elkind, M.D., Massachusetts Society for Mental Hygiene.

This course offers an unusual opportunity to hear outstanding leaders in the mental hygiene movement discuss, in simple non-technical language, principles and mechanisms of the mind which control our everyday lives. The lectures will be particularly suggestive to mothers and fathers, teachers, nurses, social workers, and doctors, since considerable attention will be given to various aspects of mental hygiene in its application to children and adolescents.

But because the "child is father to the man" everyone should be interested in the personal applications of the course. Psychiatrists recognize that a useful understanding of adult human behavior depends largely upon the study of man in the developing stages of childhood and adolescence.

PROGRAM

February 1—"The Human Mind—Personal Applications of Mental Hygiene."
Karl Menninger, M.D., Menninger Clinic and Hospital, and Southard School, Topeka, Kansas.

February 8—"The Young Child's Needs."
William E. Blatz, M.D., Professor of Psychology, University of Toronto; Director of St. George's School for Child Study, Toronto.

February 15 — "Normal Youth and Its Everyday Problems."
Douglas A. Thom, M.D., Professor of Psychiatry, Tufts Medical School, and Harvard Medical School.

February 29—"How Bad Are 'Bad' Boys?"
Samuel W. Hartwell, M.D., Director, Worcester Child Guidance Clinic; Instructor in Mental Hygiene, Simmons College School of Social Work.

March 7—"Mental Hygiene in the Schools."
Bruce Robinson, M.D., Director of Child Guidance, Public Schools, Newark, New Jersey.

March 14—"The Importance of the Teacher's Mental Health."
Van Norman Emery, M.D., Institute of Human Relations, Yale University.

March 21 — "Parental Attitudes Reflected in the Home."
George H. Preston, M.D., Commissioner of Mental Hygiene, Baltimore.

March 28—"Crime in the Present Day."
A. Warren Stearns, M.D., Dean of Tufts Medical School: Commissioner of Correction for Massachusetts.

Enrollments for this course may be made at the University Extension office, Room 217, State House, or at the first meeting of the class.

UNITED STATES CIVIL SERVICE EXAMINATION

The United States Civil Service Commission announces the following-named open competitive examination:

Cytologist

Applications for the position of cytologist must be on file with the U. S. Civil Service Commission at Washington, D. C., not later than February 9, 1932.

The examination is to fill a vacancy in the U. S. Public Health Service, for duty at Boston, Mass. The duties will be to conduct research on the growth of normal and malignant cells in vitro; to study the morphology of cells; to coöperate in radiometric studies; and to conduct other studies in cytology as may seem advisable in connection with cancer investigations.

The entrance salary for the position now vacant is not to exceed $4,200 a year.

Competitors will not be required to report for examination at any place, but will be rated on their education, training, and experience.

Certain specified education and experience required.

Full information may be obtained from the Secretary of the United States Civil Service Board of Examiners at the post office or customhouse in any city or from the United States Civil Service Commission, Washington, D. C.

CORRECTION

The spelling of the name of Dr. Dretler in the notice of his appointment (our issue of January 14) was incorrect. The notice should have read Dr. Lewis R. Dretler has been appointed to the position of resident surgeon at the Boston City Hospital.

REMOVALS

Saul M. Marcus, M.D., announces his temporary removal from 67 Main Street, Peabody, Massachusetts, to 132 East 19th Street, New York, N. Y.

Charles Rice, M.D., announces the removal of his office and residence from 1232 Blue Hill Avenue, Mattapan, to 1272 Blue Hill Avenue, Mattapan, Massachusetts.

RADIO HEALTH MESSAGES

January-February-March, 1932

Sponsored by the Public Education Committee of the Massachusetts Medical Society and the Massachusetts Department of Public Health.

Courtesy WBZA. Thursdays at 4:50 P. M.

February

4 Health in Industry
11 Growing Strong Teeth
18 The Common Cold
25 Whooping Cough

March

3 The Psychology of the Crippled Child
10 Personal Rights vs. Public Safety
17 Electrical Hazards in the Home
24 Can High Blood Pressure Be Avoided?
31 Rose Cold and Hay Fever

State House Broadcast

Sponsored by the Massachusetts Department of Public Health.

Courtesy WEEI. Fridays at 12:30 P. M.

Health matters of public interest discussed by the Division Directors of the Department.

Radio Health Forum

Queries from the public are answered under the sponsorship of the Department of Public Health.

Courtesy WEEI. Fridays at 4:50 P. M.

Questions on Health and Prevention of Disease may be sent to: Radio Health Forum, State Department of Public Health, State House, Boston.

TWO AWARDS

The New England Society of Psychiatry, at its next Spring meeting, will make two awards, one of $100.00 and one of $50.00, to the writer (or writers) of the best papers published during the calendar year of 1931 embodying *research in psychiatry* by a younger worker (or workers). Physicians, psychologists, social workers, or others are eligible. Membership in the Society is not a requisite.

Writers who have once received an Award are not again eligible. Seasoned writers, senior physicians, or heads of departments in which there are junior workers, while not inevitably excluded, will not generally be regarded as eligible for the Awards.

The work on which the papers are based should preferably have been done in New England or by workers now living in New England.

The papers will be examined by a Committee of three members who are accustomed to reviewing papers, and by the Executive Committee of the Society. They will be judged on the basis of their scientific quality.

Reprints of articles or marked copies of journals in which the articles appeared should be sent before February 1, 1932, to the Secretary of the Society.

Superintendents of institutions, public or private, for the care of mental patients in New England are requested to post this notice and send to the Secretary a list of such papers published by the members of his staff as he thinks entitled to be considered for the Awards.

Harlan L. Paine, M.D., *Secretary.*

North Grafton, Mass.

REPORT AND NOTICES OF MEETINGS

ANNUAL MEETING OF THE BOSTON MEDICAL LIBRARY

The annual meeting of the Boston Medical Library convened at the Medical Library on the evening of January 19. The reports of the several officers were read and accepted. The especial interest of the business session was centered in the report of the Treasurer, which showed a deficit in the cost of maintenance, necessitating the formulation of plans essential to maintaining the important functions of the Library.

The list of officers elected is as follows:

President: Dr. John W. Bartol.

Vice-Presidents: Dr. Homer Gage, Dr. Daniel F. Jones, Dr. George G. Sears.

Secretary: Dr. Horace Binney.

Treasurer: Dr. Richard G. Wadsworth.

Librarian: Dr. Charles F. Painter.

Following the business session, Professor John F. Fulton, of Yale University Medical School, delivered an interesting address under the title: "Haller and the Humanization of Bibliography." This paper will be published in the *Journal* at an early date.

It is remarkable that this large and important Library finds it necessary to concentrate on its financial needs, for it should have the generous support of the community.

BOSTON SURGICAL SOCIETY, INC.

All members of the profession, with their wives, are invited to a special meeting of the Boston Surgical Society to be held on Monday evening, February 1, 1932, at 8:30 P. M., at the John Hancock Hall, 90 St. James Avenue, Boston. At this meeting the Henry Jacob Bigelow medal will be awarded to Dr. John M. T. Finney of Baltimore, and he will respond with an oration on "Changing Methods in Surgery."

RICHARD H. MILLER, *Secretary.*

FRED B. LUND, *President.*

WATERTOWN PHYSICIANS' SOCIETY

The monthly meeting of the Watertown Physicians' Society will be held Monday, February 1, at 128 Mt. Auburn Street, Watertown.

Dr. Charles H. Lawrence will be the speaker of the evening.

Subject: Practical Endocrinology.

Interested physicians are invited to attend.

Meeting at 8:30 P. M.

EUGENE F. GORMAN, M.D., *Secretary.*

HARVARD MEDICAL SOCIETY

The next meeting of the Harvard Medical Society will be held in the Peter Bent Brigham Hospital Amphitheatre (Van Dyke Street entrance), Tuesday evening, February 9, at 8:15 o'clock.

PROGRAM

Usual exhibition of cases.

Further Studies of Hypothalmic Function, by Professor John Beattie of McGill University.

Medical students and physicians are cordially invited to attend.

JOHN HOMANS, *Secretary.*

MASSACHUSETTS GENERAL HOSPITAL

A Clinical Meeting of the Staff of the Massachusetts General Hospital will be held in the Moseley Memorial Building on Thursday, February 11, 1932, at 8:15 P. M.

PROGRAM

1. Presentation of Cases.
2. Lymphoma of Stomach — Dr. William C. Martin.
3. The So-Called Prepyloric Ulcer—Dr. Audrey O. Hampton.
4. Surgical Results in Carcinoma of Stomach—Dr. Langdon Parsons.

Physicians, medical students and nurses are cordially invited to attend.

COMMITTEE ON HOSPITAL MEETINGS.

NEW ENGLAND HEART ASSOCIATION

CARDIAC COURSE

The fourth meeting of the Cardiac Course of the New England Heart Association for the season 1931-1932 will be held in the Boston Medical Library (John Ware Hall) on Wednesday, February 3, at 4:30 P. M.

Bacterial Endocarditis

1. Pneumococcus Endocarditis. Dr. Frederick T. Lord.
2. Other Types of Acute Bacterial Endocarditis. Dr. Cadis Phipps.
3. Streptococcus Viridans. Dr. Hyman Morrison.
4. Discussion. Dr. James Hitchcock.

All who are interested are invited to attend.

PAUL W. EMERSON, *Secretary.*

GREATER BOSTON MEDICAL SOCIETY

A joint meeting of the Greater Boston Medical Society and the Beth Israel Hospital will be held on Tuesday, February 2, 1932, at 8:15 P. M., at the Beth Israel Hospital.

PROGRAM

Recent Developments in Endocrinology. Roy G. Hoskins, M.D., Neuro-Endocrine Research, Harvard Medical School.

Discussion. Joseph C. Aub, M.D., Huntington Memorial Hospital.

Physicians and students are cordially invited.

BERNARD I. GOLDBERG, M.D., *Secretary.*

483 Beacon Street, Boston, Mass.

BELMONT MEDICAL SOCIETY

The next meeting of the Belmont Medical Society will be held on Friday, January 29, at 8:15 P. M., at All Saints' Parish House, Clark Street, Belmont. The speaker will be Dr. William Reid Morrison, Associate Professor of Surgery, Boston University School of Medicine, and Visiting Surgeon, Boston City Hospital. Subject: Stomach Surgery (with motion pictures). New officers will be installed, President, Dr. E. W. Small; Secretary, Dr. Fleming.

STEPHEN J. MALONE, M.D., *Secretary.*

THE NEW ENGLAND HOSPITAL ASSOCIATION

TENTH ANNUAL MEETING

February 4-5-6, 1932
Copley-Plaza Hotel
Boston, Mass.

Thursday, February 4.

6:00 P. M.—Informal Dinner.

8:00 P. M.—Informal Theatre Party.

Miss Vera Houston, Asst. Supt., Newton Hospital, Newton, Mass., in charge of arrangements.

Friday morning, February 5.

D. L. Richardson, M.D., Supt., City Hospital, Providence, R. I., Presiding.

8:30—Registration.

9:15—Official Opening of Conference by the President.

Mr. James A. Hamilton, Supt., Mary Hitchcock Memorial Hospital, Hanover, New Hampshire.

9:30—"The Relation of the Record Librarian to the Superintendent, the Hospital, and the Community."

Mrs. Grace W. Myers, President of the Massachusetts State Association of Record Librarians.

"What Does a Hospital Expect of a Record Librarian?"

Charles H. Pelton, M.D., Asst. Supt., Boston City Hospital, Boston, Massachusetts.

Discussion.

10:15—"Shall Trays Be Served by Nurses or Dietitians?"

Miss Margaret McGovern, B.S., Head Dietitian, Boston City Hospital, Boston, Massachusetts.

Discussion.

11:00—"Purchasing."

Major George J. Cronin, State Purchasing Agent, Commonwealth of Massachusetts.

Discussion, Mr. Sidney M. Bergman, Asst. Director, Beth Israel Hospital, Boston, Massachusetts.

11:45—Round Table Discussion.

Conducted by Mr. Scott Whitcher, Supt., St. Luke's Hospital, New Bedford, Massachusetts.

12:15—Adjournment.

Friday Noon Luncheon—12:30.

W. Franklin Wood, M.D., Asst. Director, Massachusetts General Hospital, Presiding.

"Hospitals and Health Departments."

George H. Bigelow, M.D., Commissioner of Public Health, Commonwealth of Massachusetts.

Friday Afternoon.

Miss Miriam Curtis, Supt., Cooley Dickinson Hospital, Northampton, Mass., Presiding.

2:15—"A Plan for Group Nursing."

Miss Ella Hasenjaeger, Director of Nursing, Grace Hospital, New Haven, Conn.

Discussion, Miss Helen Wood, Acting Principal of the Training School and Superintendent of Nurses, Massachusetts General Hospital, Boston.

3:00—"The Nurses' Registry—A Nursing Service Bureau."

Miss Ella Best, Field Secretary, American Nurses' Association, New York City.

Discussion.

3:30—"Trends in General Business Conditions."

Professor H. V. Olsen, Tuck School, Dartmouth College, Hanover, New Hampshire.

4:15—"The Hospital Superintendent and Business Depressions."

Lewis A. Sexton, M.D., Supt., Hartford Hospital.

Frederic A. Washburn, M.D., Director, Massachusetts General Hospital.

4:45—Round Table Discussion.

Conducted by Mr. Scott Whitcher.

5:15—Adjournment.

Friday Evening—Banquet 6:30.

Miss Bertha Allen, Vice-President, New England Hospital Association, Newton, Mass., Presiding.

"Civilizing Civilization."

Mr. Leonard W. Cronkhite, Member of the Board of Directors of the Massachusetts Branch of the League of Nations Association.

"Magic As a Hobby."

Professor Raymond.

Saturday Morning, February 6.

Thomas S. Brown, M.D., Supt., Mary Fletcher Hospital, Burlington, Vermont, Presiding.

9:30—"What Legislation Has Done for our Hospitals."

R. L. Leak, M.D., Supt., Connecticut State Hospital, Middletown, Connecticut.

10:00—"Proposed Legislation in Massachusetts."

H. M. Pollock, M.D., Supt., Massachusetts Memorial Hospitals.

J. B. Howland, M.D., Supt., Peter Bent Brigham Hospital.

10:30—"The Hospital and Workmen's Compensation."

Mr. William W. Kennard, Chairman, Industrial Accident Board.

Discussion.

11:00—"The Hospital and the Insurance Company."

James C. Graves, Jr., M.D., Surgical Director, Travelers Insurance Company, Hartford, Connecticut.

Discussion.

11:30—Round Table Discussion.

Conducted by Mr. Scott Whitcher.

12:45—Adjournment.

Saturday Noon Luncheon—1:00.

Mr. James A. Hamilton, Presiding.

Address—Mr. Paul Fesler, President, American Hospital Association, Minneapolis, Minn.

Election of Officers.

Saturday Afternoon.

2:30—Inspection of New Features of Hospital Construction and Equipment.

W. Franklin Wood, M.D., Asst. Director, Massachusetts General Hospital, in charge of arrangements.

BOSTON TUBERCULOSIS ASSOCIATION

The annual meeting of the Boston Tuberculosis Association will be held at 35 Tyler Street, February 3, at 4 P. M. Dr. John B. Hawes, 2d, will report on progress, followed by Dr. Edward O. Otis, who will give an address.

SOCIETY MEETINGS
CONGRESSES AND CONFERENCES

January 29—Belmont Medical Society. See page 205.

February 1—American Heart Association. See page 101, issue of January 14.

February 1—Boston Surgical Society. See page 204.

February 1—Watertown Physicians' Society. See page 204.

February 1-5—An Institute for Tuberculosis Workers. See page 146, issue of January 21.

February 2—Greater Boston Medical Society. See page 204.

February 3—Boston Tuberculosis Association. See notice above.

February 3—New England Heart Association. See page 204.

February 4—Medical Clinic at the Peter Bent Brigham Hospital. See page 202.

February 4, 5, 6—New England Hospital Association. See page 205.

February 9—Harvard Medical Society. See page 204.

February 11—Massachusetts General Hospital. See page 204.

February 12 - May 6—William Harvey Society. See page 745, issue of October 8.

March - April, Autumn — International Postgraduate Courses in Berlin. See page 1169, issue of December 10.

April 4-8—The American College of Physicians. See notice on page 1232, issue of June 4.

May 9-13—American Medical Association, New Orleans, La.

June 8, 9, 10—Massachusetts Medical Society, Hotel Statler, Boston.

October 24-27—American Public Health Association. See notice on page 1321, issue of December 31.

October 24-28—Inter-state Postgraduate Medical Association of North America. See page 39, issue of January 7.

DISTRICT MEDICAL SOCIETIES

Essex North District Medical Society

May 4—Annual meeting at Lawrence.

Essex South District Medical Society

February 3, Wednesday—Council Meeting, Boston.

February 10, Wednesday—Hawthorne Hotel, Salem. Dinner 7 P. M. Speakers: Dr. Lincoln F. Sise and Dr. Harry H. Germain. Subject: Selection of the Anesthetic for the Patient and Operation. Dr. Sise to speak from the viewpoint of the Anesthetist, and Dr. Germain from the viewpoint of the Surgeon.

March 2, Wednesday—Lynn Hospital. Clinic 5 P. M. Dinner 7 P. M. Subject to be announced later. Speaker: Dr. Elmer W. Barron, Boston.

April 6, Wednesday—Essex Sanatorium, Middleton. Clinic 5 P. M. Dinner 7 P. M. Speaker: Dr. Arthur P. Wakefield, State Department of Health. Subject: 10-Year Tuberculosis Program in the Public Schools.

May 5, Thursday—Censors' Meeting, Salem Hospital, 3:30 P. M.

May 10, Tuesday—Annual Meeting. The Tavern, Gloucester. Speaker and subject to be announced later. Ladies invited.

Franklin District Medical Society

Meeting will be held on the second Tuesday of March and May at the Weldon, Greenfield, at 11 A. M.

CHARLES MOLINE, Secretary.

Middlesex East District Medical Society

At a meeting of the executive committee the following schedule for the Middlesex East District Medical Society was arranged:

March—At Reading.

May—At Woburn.

Meetings on the second Wednesday of each month unless otherwise announced.

Norfolk District Medical Society

February 23—Place to be announced. Clinico-Pathological meeting, Dr. Frank S. Cruickshank, and Dr. J. W. Budd of the Medical and Pathological Staff of the Boston City Hospital.

March 29—Place to be announced. Boston Public Health Meeting. Speakers, Honorable James M. Curley, Dr. Francis X. Mahoney, Dr. Charles Wilinsky, Dr. W. H. Griffin.

May—Annual Meeting, date and place to be announced.

May 5—Censors' Meeting for examination of candidates. Roxbury Masonic Temple, 171 Warren Street, Roxbury, 4 P. M. Fee $10.00 payable at time of examination. All candidates will have applications in the hands of the secretary one week prior to this date. All candidates from Medical Schools not on approved list of Society must have application complete two weeks prior to date of examination.

F. S. CRUICKSHANK, Secretary.

Norfolk South District Medical Society

February 4—This meeting will be held at the Quincy City Hospital. The program will be furnished by the members of the hospital staff.

March 3—Speaker: Roderick Heffron, M.D. Subject: Pneumonia.

April 7—To be announced later.

May 5—Annual meeting.

The time of all meetings is 12 o'clock noon. All meetings, except February 4, will be held at the Norfolk County Hospital, South Braintree. Censors will meet on May 5 at 11:15 A. M. at the Norfolk County Hospital.

N. R. PILLSBURY, Secretary.

Suffolk District Medical Society

February 24—Clinical Program, the Children's Hospital.

March 30—Clinical Program, New England Deaconess Hospital.

April 27—The Annual Meeting, Boston Medical Library. Election of Officers.

The Medical Profession is cordially invited to attend all of these meetings.

GEORGE S. DERBY, M.D., President.*
LELAND S. McKITTRICK, M.D., Secretary.
HILBERT F. DAY, M.D., Boston Medical Library.

Worcester District Medical Society

Wednesday evening, February 10—Worcester State Hospital. 6:30—Dinner, complimentary by the Worcester State Hospital. 7:45—A psychiatric program to be announced later.

Wednesday evening, March 9 — Memorial Hospital, Worcester, Mass. 6:30—Dinner, complimentary by Memorial Hospital. 7:45—A pediatric meeting with subjects to be announced later.

Wednesday evening, April 13—Grafton State Hospital, North Grafton, Mass. 6:30—Dinner, complimentary by Grafton State Hospital. 7:45—Program to be announced later.

Wednesday afternoon and evening, May 11—Annual Meeting. Program to be announced later.

ERWIN C. MILLER, Secretary.

*Deceased.